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130th anniversary of virology

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130 years ago, in 1892, our great compatriot Dmitry Iosifovich Ivanovsky (1864–1920) discovered a new type of pathogen – viruses. Viruses have existed since the birth of life on Earth and for more than three billion years, as the biosphere evolved, they are included in interpopulation interactions with representatives of all kingdoms of life: archaea, bacteria, protozoa, algae, fungi, plants, invertebrates, and vertebrates, including the *Homo sapiens* (Hominidae, *Homininae*).

Discovery of D.I. Ivanovsky laid the foundation for a new science – virology. The rapid development of virology in the 20th century was associated with the fight against emerging and reemerging infections, epidemics (epizootics) and pandemics (panzootics) of which posed a threat to national and global biosecurity (tick-borne and other encephalitis, hemorrhagic fevers, influenza, smallpox, poliomyelitis, HIV, parenteral hepatitis, coronaviral and other infections). Fundamental research on viruses created the basis for the development of effective methods of diagnostics, vaccine prophylaxis, and antiviral drugs. Russian virologists continue to occupy leading positions in some priority areas of modern virology in vaccinology, environmental studies oz zoonotic viruses, studies of viral evolution in various ecosystems, and several other areas. A meaningful combination of theoretical approaches to studying the evolution of viruses with innovative methods for studying their molecular genetic properties and the creation of new generations of vaccines and antiviral drugs on this basis will significantly reduce the consequences of future pandemics or panzootics. The review presents the main stages in the formation and development of virology as a science in Russia with an emphasis on the most significant achievements of soviet and Russian virologists in the fight against viral infectious diseases.

Keywords: *virology; D.I. Ivanovsky; smallpox; poliomyelitis; emerging infections; reemerging infections; influenza; tick-borne encephalitis; arboviruses; HIV; parenteral hepatitis; COVID-19; vaccines*

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130 лет вирусологии

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130 лет назад, в 1892 г., нашим великим соотечественником Дмитрием Иосифовичем Ивановским (1864–1920) открыт новый вид патогенов – вирусы. Вирусы существуют с момента зарождения жизни на Земле и на протяжении более 3 млрд лет по мере эволюции биосферы включены в межпопуляционные взаимодействия с представителями всех царств жизни: архей, бактерий, простейших, водорослей, грибов, растений, беспозвоночных и позвоночных животных, позднее включая вид *Homo sapiens* (Hominidae, *Hominae*). Открытие Д.И. Ивановского положило начало новой науке – вирусологии, бурное развитие которой в XX в. было связано с борьбой с новыми и возвращающимися (emerging-reemerging) инфекциями, эпидемии (эпизоотии) и пандемии (панзоотии) которых создавали угрозу национальной и глобальной биобезопасности (клещевой и другие энцефалиты, геморрагические лихорадки, грипп, оспа, полиомиелит, ВИЧ, парентеральные гепатиты, коронавирусные и другие инфекции). Фундаментальные исследования свойств вирусов заложили основу для разработки эффективных методов диагностики, вакцинопрофилактики и противовирусных лечебных препаратов. Отечественные вирусологи продолжают занимать ведущие позиции по некоторым приоритетным направлениям современной вирусологии, в частности по вакцинологии, мониторингу формирования популяционного генофонда вирусов в процессе эволюции в различных экосистемах и ряду других направлений. Осмысленное сочетание теоретических подходов изучения эволюции вирусов с инновационными методами исследований их молекулярно-генетических свойств и создание на этой основе новых поколений вакцин и противовирусных препаратов обеспечат существенное снижение последствий грядущих пандемий (панзоотий), возможность возникновения которых в будущем чрезвычайно высока. В обзоре представлены основные этапы становления и развития вирусологии как науки в России с акцентом на наиболее значимых достижениях отечественных вирусологов в борьбе с вирусными инфекционными заболеваниями человека и животных.

Ключевые слова: *вирусология; Д.И. Ивановский; оспа; полиомиелит; новые инфекции; возвращающиеся инфекции; грипп; клещевой энцефалит; арбовирусы; ВИЧ; парентеральные гепатиты; COVID-19; вакцины*

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Introduction

The established system of studies in infectious diseases is based on the etiological principle: The infection-causing pathogens are studied by three sciences – bacteriology, virology, and mycology, which are combined under the umbrella term “microbiology”. The leading virologists of the mid-twentieth century such as Viktor Mikhailovich Zhdanov (1914–1986), Joseph Melnick (United States, 1914–2001), Peter Wildy (Great Britain, 1920–1987) and Nils Oker-Blom (Finland, 1919–1995) spearheaded the establishment of the Virology Division at the International Union of Microbiology Societies (IUMS), which holds congresses every 3 years. The virological section of these congresses is most active and best represented.

In the modern classification, viruses represent a separate, though not formally designated domain analog – Viruses, along with three main domains of life: Archaea, Bacteria and Eukarya. Within the domain, viruses are grouped into six main realms, 10 kingdoms, 17 phyla, 65 orders, 233 families and 2,606 genera including more than 10,000 described species[1].

[1]Current ICTV Taxonomy Release. Taxonomy Browser. Available at: https://ictv.global/taxonomy.

The birth of virology

The empirical period of virology development dates back to the mid-19th century when Edward Jenner (1729–1823) used the cowpox lesion exudate to inoculate a patient against smallpox, and Louis Pasteur (1822–1895) developed the first rabies vaccine 14 years before the discovery of the first animal virus.

The science of virology continued to gather pace during the last decade of the 19th century, and the outstanding role in its development belongs to the scientists who worked with the model of the tobacco mosaic virus (TMV), which, following the modern classification, belongs to the genus *Tobamovirus*, the family Virgaviridae: the German chemist Adolf Mayer (1843–1942), the Russian botanist Dmitri Iosifovich Ivanovsky (1864–1920) and the Dutch microbiologist Martinus Willem Beijerinck (1851–1931). A. Mayer gave a name to the tobacco disease and identified its infective nature [1]. In his five-year research cycle started in 1887, D.I. Ivanovsky was the first to point at two different diseases with fungal and unknown etiology. The 28-year-old researcher published the results of his first experiments in the article "On Two Diseases of Tobacco" in the Agriculture and Forestry journal [2] as well as in its German language version in the collection of research papers issued by the St. Petersburg Imperial Academy of Sciences [3] in 1892. His concept about new biological life form was further developed in his doctoral dissertation "Mosaic Disease in Tobacco" [4].

D.I. Ivanovsky was the first to identify and describe the main characteristics typical of the new, unknown life form:

1) the ability to replicate only in a living organism – a plant, tobacco leaves (obligate parasites);

2) as opposed to microbes, the inability to replicate in a standard cell-free nutrient agar medium;

3) the corpuscular nature of the intracellular agent (*contagium vivum fixum*);

4) the infectious nature of a biological entity (contagiousness);

5) small sizes and the ability to pass through bacterial porcelain filters (a filter-passing infectious agent).

The Dutch scientist M. Beijerinck, who made similar observations 6 years after D.I. Ivanovsky had published the results of his studies in 1892, acknowledged the priority of the Russian scientist's findings and confirmed it in his famous letter to D.I. Ivanovsky in 1899 [5, 6]: "I confirm that the priority of the test using filtration through candles (Chamberland candles – *Author's note*), as I have found, belongs to Mr. Ivanovsky. When I was writing my paper, I was not aware of tests of Mr. Ivanovsky or Mr. Polovtsev."

Unlike the Russian scientist, the Dutch researcher misinterpreted his findings in his works, describing the agent causing the tobacco disease as a soluble poison, a contagious living fluid (*contagium vivum fluidum*). Following his misguided assumption, M. Beijerinck offered the inaccurate term "virus" (liquid poison) to define the new unknown infectious agent; the incorrect term was extensively used in scientific literature and entered the general lexicon [7].

Thus, the credit for the discovery of the new infectious agent of corpuscular nature, which represented a new life form, and international recognitions are rightfully given to the Russian scientist D.I. Ivanovsky. Fifty years later, the virologist and Nobel prize laureate Wendell M. Stanley wrote that "I believe that his relationship to viruses should be viewed in much the same light as we view Pasteur's and Koch's relationship to bacteriology. There is considerable justification for regarding Iwanowski as the father of the new science of virology" [8].

D.I. Ivanovsky's contribution holds a prominent place in the history of Russian science. The scale of recognition of his ideas and their impact on development of the Russian and world science bring his name to the top list of such outstanding scientists of Russia as M.V. Lomonosov, I.I. Mechnikov, I.P. Pavlov, D.I. Mendeleev, N.I. Vavilov, K.E. Tsiolkovsky and others. Thanks to the genius of D.I. Ivanovsky, Russia became the unquestionable birthplace of virology; the historical memory of this prominent scientist and his contribution should be cherished and made known to future generations in Russia, starting from school.

Acknowledging the international significance of D.I. Ivanovsky's discoveries and importance of the virological science for the country, the Government of the Soviet Union issued the resolution honoring the memory of D.I. Ivanovsky and established an award named after him in 1950. Today, the award has been forgotten in Russia. It may be time to revive it with the support of the Russian Academy of Sciences and to establish a prestigious international award named after D.I. Ivanovsky as well as to issue postage stamps commemorating the 130th anniversary of the first groundbreaking research article written by D.I. Ivanovsky in 1892 and laying the foundation for virology, a new science.

The infancy period was not long, and virology stepped into a stage of maturity at the end of the 19th century with the first description of viral infectious diseases of animals – foot-and-mouth disease by the German scientist Friedrich Loeffler (1852–1915) [9] and humans – yellow fever by the U.S. Army surgeon Walter Reed (1851–1902) [10].

Development of virology – history of emerging and re-emerging infections

At the stage of their research, newly discovered viral infections of plants, animals and humans should be classified as the so-called emerging and re-emerging infections [11, 12]. The evolution of pathogens causing these infections should be given close scientific attention, as it represents the history of species ecology. Ecology, as defined by its founder (1866) Ernst Heinrich Haeckel (1834–1919), studies interactions among species and with their physical environment [13]. Later, the concept was expanded, including multi-species communities – ecosystems [14–16]. It has been found that these interactions take place at the molecular and genetic level during formation of the population gene pool within the ecosystem [17]. The type of the interactions and their consequences are encoded by the common protected population gene pool of species [18]. In viruses, its formation takes doz-

ens, hundreds, thousands, or millions of years, and involves close interaction with elements of the biosphere in the existing environment. This laid the foundation for molecular ecology of viruses.

The studies of the yellow fever virus belonging to the ecological group of arboviruses demonstrated the pathogen's capability of (and need for) cross-taxon transmission from arthropod vectors (Arthropoda) (arachnids (Arachnida) ticks and insects (Insecta), dipterans (Diptera) – mosquitoes, sand flies, midges) to vertebrate hosts (Vertebrata) of various taxa (Reptilia, Amphibia, Aves, Mammalia). During the evolution of viruses, the cross-taxon transmission resulted in transmission of zoonotic viruses to the *Homo sapiens* population and development of all human infectious diseases, which turned into zooanthroponoses and anthroponoses.

Later, it was found that viruses can infect all elements of the biosphere – archaea, bacteria, protozoa, algae, plants, fungi, invertebrates and vertebrates, animals and humans who appeared much later [19, 20]. This process lasted for around 3.5 billion years and involved evolution of the living environment of viruses and their hosts – the biosphere. Its milestones were the emergence of prokaryotes during the Archean, eukaryotes in the Proterozoic, emergence of the main types of animals during the Cambrian period, emergence of fish in the Silurian period, amphibians in the Devonian period, reptiles in the Carboniferous – Jurassic periods, insect-eating mammals and birds in the Cretaceous period of the Mesozoic Era, bats in the Tertiary period of the Cenozoic, rodents in the Paleocene. All these events preceded the emergence of humans. The first representatives of the order primates appeared during the Paleocene. The oldest known remains of human ancestors (the family Pongidae) date back to the Oligocene. Hominids (the family Hominidae) appeared during the Pliocene, while hominins (the subfamily Homininae, genus Homo) appeared during the Pleistocene of the Quaternary period. Ancestors of *H. sapiens* started interacting with animal virus populations at the beginning of the Holocene period. Having started 10–20 thousand years ago, domestication of animals propelled the spread of animal viruses to human population [17, 21]. The evolution of viruses continuing in natural ecosystems and emerging population gene pools pose a risk of new genetic clusters capable of transmission to the human population and causing new infections. The process of virus-host interaction in the changing living environment leads to changes in the population gene pool that has to adapt to these changes. Therefore, the main patterns of virus retention in the biosphere require systemic monitoring [11, 12, 17–22].

130 years after D.I. Ivanovsky described the first pathogen of the viral infection, the Russian virology continues to stay at the forefront of modern virology, taking advantage of innovative technology and doing research in priority areas, including evolution of pathogens causing emerging and re-emerging infections, which pose global threat to safety of the population and the environment. Emerging and re-emerging infections are a "dormant volcano", which can wake up any time. Viruses, especially those transmitted by respiratory routes (influenza viruses, poxviruses, coronaviruses), will "show their teeth" to the population of our planet in the foreseeable future.

The years of D.I. Ivanovsky's research work were the golden age of the St. Petersburg University with such eminent scientists as D.I. Mendeleev, A.M. Butlerov, V.V. Dokuchaev, I.M. Sechenov and Ivanovsky's scientific supervisors – A.S. Famitsyn and A.N. Beketov. It was a thriving period of Russia, which was interrupted by the events of 1917 and the subsequent Civil War. Sparks of the Russian virology were faintly glowing among smoldering ruins. In the late 1920s–1930s, the Russian virology started reviving gradually.

Variola virus (Poxviridae: *Orthopoxvirinae: Orthopoxvirus*)

In the 1920s, Russia and other countries were hit by devastating outbreaks caused by the variola virus (Variola major virus), with up to 200 thousand cases a year and the death rates reaching 40–60%. The mass vaccination owes its success to the timely organized production of the vaccine and to the mandatory vaccination system; the incidence of infection was reduced to zero in 1936. In 1958, at the 11th World Health Assembly, V.M. Zhdanov called on the member countries to undertake a global initiative to eradicate smallpox. More than 1.5 billion vaccine doses were donated by our country for implementation of the initiative supervised by the eminent American epidemiologist Donald Henderson. The estimated cost of the smallpox eradication campaign was 300 million dollars, while the number of saved lives was around 50 million, i.e. 6 dollars per human life [23]. Many Russian virologists took part in the implementation of the program, with S.S. Marennikova leading the list. S.N. Schelkunov performed the first-time sequencing of the variola virus genome [24]. The world's last case of smallpox was reported in Somalia in October 1977 [25, 26]. However, smallpox was eradicated only among people. There are many natural clusters – from tropical deserts to subarctic tundra – of genetically related viruses lurking in rodents for millions of years [17].

The virus may come back, as it happened at least three times in the past [17, 27–30]. The growing number of monkeypox outbreaks among humans in Africa have triggered concern in the recent years [31–35]. Studies show that rodents are a natural reservoir of the virus – at least 4 species of squirrels (Rodentia: Sciuridae): *Funisciurus lemniscates*, *F. anerythrus*, *Heliosciurius rufobranium* and *H. gambianus*. These animals have been identified as virus carriers, while having asymptomatic infection [36]. Monkeys of the genera *Cercopithecus*, *Colobus* and *Cercocebus* act as intermediate hosts and the main source of human infection. The United States saw a monkeypox outbreak of dozens of cases in 2003 [37–39]. Most of the people became ill after having contact with rodents, prairie dogs *Cynomys ludovicianus*, which are kept as pets. Before they were sold, pet prairie dogs had contact with rodents and civets imported from Africa, many of which died.

Brazil, India, and Pakistan report outbreaks among domestic animals and people who have contact with them;

these outbreaks are caused by zoonotic poxviruses associated with rodents [40]. It was found that camelpox and taterapox viruses, which are evolutionary closely related to the smallpox virus, had the common ancestor around 4 thousand years ago [30].

The pandemic spread of monkeypox started in 2022. According to WHO, from January 1 to September 1 in 2022, more than 50,000 cases in 101 countries were reported [41], while prior to the global outbreak, 4,522 cases had been reported in 9 African countries and 72 cases had been reported in the United States during the monitoring period (from 1970 to 2007). Three deaths were reported (all of them in Africa), i.e. the mortality rate is 0.006% (similar to the rates typical of the seasonal flu) compared to the average mortality rate of 9.8%, which had been observed during the previous outbreaks in Africa. Russia reported only two cases (July – September 2022). A few cases were reported worldwide in January – April, then their number surged in June – July. 99.5% of reported cases are among men, including 60% of men who have sex with men, 41% of HIV positive patients. Clinical symptoms include generalized rashes throughout the body (81%), fever (50%), a rash on or near the genitals (41%); the incubation period can range from 7–21 days (usually 12 days). Genetically, the virus belongs to the West African clade.

Monkeypox is diagnosed using a polymerase chain reaction (PCR). The illness typically lasts 2–4 weeks [41]. Cidofovir (an acyclic phosphate analog cytidine-5'-monophosphate) approved for clinical use in 1996 is recommended for treatment and prevention [42, 43]. The medication is effective, but the drug-induced nephrotoxicity is a major concern requiring monitoring the renal function. Recently developed lipophilic prodrugs are more effective and less toxic, for example, hexa-decyloxypropylcidophosphate. The antiviral compound developed in the United States is ST-246 having 50% effective concentrations of 0.067 μM against variola virus and < 0.04 μM against monkeypox virus [44]. The tests involving nonhuman primates showed that the administration of ST-246 at a dose of 10 mg/kg/day for 14 days resulted in 100% protection against smallpox, being comparable to an oral dosage of 400 mg/day for 2 weeks in humans.

The use of live smallpox vaccines in critical situations can cause severe complications in 25% of the vaccinated individuals; therefore, there have been developed third and fourth-generation vaccines such as Imvamune (Bavarian Nordic, Germany), Acam 2000, IMVAMUNE and others without any serious adverse effects [45–47].

All the facts listed above imply the theoretical probability that pandemics can occur again due to the spillover of the smallpox virus or a related virus from a natural reservoir. This scenario would result in catastrophic consequences, considering that 40 years after the vaccination was discontinued worldwide, the population has hardly any immunity against smallpox [48]. The risk of this group of viruses being used for terroristic purposes cannot be excluded. Therefore, the national stockpile must contain supplies of safe and effective antivirals and vaccines for treatment and prevention [49].

Vaccines and antivirals

Ilya Ilyich Mechnikov (1845–1916) and Nikolay Fyodorovich Gamaleya (1859–1949) pioneered rabies research in Russia. The world's second Pasteur anti-rabies station (the first one was opened in Paris) was opened in Odessa in 1886; by 1935, hundreds of such stations were operating across the country. New rabies vaccines have been developed [50]; special attention is given to monitoring of the virus spread as well as to the molecular and genetic analysis of the circulating strains [51].

The studies on arboviruses, which are conducted in the country, will be discussed later. Here, we are going to focus on the greatest achievements of virologists in development of vaccines against deadly viral infections that have claimed millions of human lives [23, 52–56].

In the late 1930s, American and French scientists independently developed vaccines against yellow fever; the first influenza vaccine was developed in the United Kingdom in 1942. Vaccination against measles, rubella and mumps protects health and saves lives of millions of children throughout the world [23, 52–54]. A significant contribution to development of Russian vaccines for children was made by A.A. Smorodintsev (1901–1986), M.P. Chumakov (1909–1993), O.G. Andzhaparidze (1920–1996), V.V. Zverev, N.V. Yuminova and research teams led by them.

The polio pandemic necessitated development of a vaccine protecting against the severe disease. In 1953, Jonas Salk (1914–1995) created an inactivated polio vaccine, and in 1956, Albert Sabin (1907–1993) developed a live attenuated polio vaccine administered orally. A considerable contribution to the polio vaccine research was made by A.A. Smorodintsev and M.P. Chumakov, who was appointed the director of the Institute of Poliomyelitis and Viral Encephalitis of the USSR Academy of Medical Sciences in 1955. Within an unprecedentedly short time, large-scale production of vaccines from attenuated Sabin strains was launched; controlled epidemiological trials were conducted to study the efficacy and safety of the vaccine. The epidemic situation in the country had been eliminated by 1960. Large vaccine supplies were donated free of charge to Japan and many other countries, which were able to significantly decrease the incidence rates. Young virologists, future academicians took an active part in these joint efforts, including Sergey Grigorievich Drozdov (1929–2016), Vasily Andreevich Lashkevich (1927–2018), Soslan Grigorievich Dzagurov (1925–1985), Boris Fyodorovich Semyonov (1929–2010), Marina Konstantinovna Voroshilova (1922–1986) and many others. In 1988, the World Health Assembly adopted a resolution for the worldwide eradication of polio [57]. Since July 1, 2002, no cases of polio have reportedly originated in Russia, although there have been a few imported cases. In the meantime, recently, the situation has changed for the worse in some bordering countries due to the discontinued vaccination.

Outstanding results were achieved by Russian researchers in development, evaluation of efficacy and safety of

vaccines against SARS-CoV-2 approved for commercial production. The main vaccine developers are Aleksandr Leonidovich Gintsburg, Denis Yurievich Logunov from the Gamaleya National Research Center of Epidemiology and Microbiology (NRCEM) of the Health Ministry of Russia, and Sergey Vladimirovich Borisevich from the 48th Central Research Institute of the RF Ministry of Defense received State Awards and prestigious government awards. The Sputnik V vaccine was the world's first registered vaccine against COVID-19 [58].

The Sputnik V vaccine was approved on August 11, 2020; it was based on two replication-defective human adenovirus vectors (HAdV-26 and HAdV-5) at Gamaleya NRCEM. The second Russian vaccine – peptide-based EpiVacCorona developed at the State Research Center of Virology and Biotechnology Vector is not widely used. The third Russian vaccine – CoviVac developed at the Chumakov Federal Scientific Center for Research and Development of Immune and Biological Products (FSCRDIBP) was registered on February 19, 2021 (an inactivated, Vero-cell based vaccine with Al-OH adjuvant); it was made incorporating the technology similar to the tissue-culture vaccine against tick-borne encephalitis (TBE) developed in 1963. The vaccines developed in other countries include Pfizer (approved on December 2, 2020, an RNA vaccine formulated in lipid nanoparticles), Moderna (approved on December 18, 2020, an RNA vaccine formulated in lipid nanoparticles), Astra-Zeneca (approved on December 30, 2020; the vaccine contains a replication-deficient chimpanzee adenovirus vector), Janssen (approved on February 27, 2021; the vaccine contains the replication-deficient human adenovirus vector HAdV26), inactivated vaccines with Al-OH adjuvant – Covaxin (India, January 3, 2021), QazVac (Kazakhstan, January 13, 2021), CoronaVac (China, February 6, 2021), Sinofarm (China, February 25, 2021) [23]. The vaccines helped significantly reduce incidence and death rates; in fact, they are the only powerful tool to fight against different genetic variants of COVID-19.

The above examples show the role of vaccination in the combat against viral infections. In each case, the successful outcome depends on the availability of a safe and effective vaccine. The use of vaccines is the greatest achievement of mankind; vaccines made a substantial contribution to life expectancy and quality of life.

Vaccinology as a science has come to maturity in the last decades; it deals with development of vaccines, with evaluation of their safety and efficacy [23, 53]. In the 20th century, the life expectancy increased from 32 years to 69 years, mainly due to a reduction in child mortality [23]. The National Immunization Schedule in Russia (the Decree of the RF Ministry of Health, No. 1122n, issued on December 6, 2021) includes (in reference to viral infections): the hepatitis B vaccine – the first dose of vaccine within the first hours of birth, then 1 month after the first dose and 6 months after the first dose; the polio vaccine – at ages 3 months, 4.5 months (inactivated), 6 months (oral), 18 months, 20 months, 6 years, 14 years (oral); the measles, mumps, rubella vaccine given at 12 months of age (live attenuated vaccines)[2]. The categories of people subject to mandatory vaccination against viral infections: rabies – people with high risk for rabies exposures (veterinarians, rangers); TBE – people living in or traveling to endemic areas; yellow fever – people traveling to endemic areas; hepatitis A – people living in or traveling to endemic areas; SARS-CoV-2 – high-risk groups, the military, conscripts[3].

The TBE virus was discovered in 1937, and since then, for more than 80 years, Russian virologists continued developing and improving vaccines against TBE infection; in 1937–1959, the vaccines were derived from the brain of infected white mice (postvaccinal encephalitis, 1 : 20 000) [59, 60]. In 1960, the large-scale production of the tissue-culture inactivated vaccine was organized under the supervision of M.P. Chumakov [61, 62]. The controlled epidemiological trials demonstrated its safety and high efficacy (95–98%) [63]. Currently, in Russia, the approved vaccines include the TBE vaccine, tissue-culture concentrated purified inactivated dry (KE-Moskva/TBE-Moscow) and the Tick-E-Vac vaccine developed at Chumakov FSCRDIBP of the Russian Academy of Sciences (Russia), EnceVir and pediatric EnceVir NEO manufactured by Microgen NPO of the Health Ministry of Russia (Russia), FSME-Immun and FSME-Immun Junior manufactured by Pfizer Inc. (Austria), Encepur and Encepur Kinder manufactured by GSK Vaccines GmbH (Germany). The vaccination schedule: The first two doses are administered at the interval of 1–7 months; the third dose is given one year after the first doses; revaccination is required every 3 years. The Russian vaccines provide effective protection against all genotypes of the TBE virus and the Omsk hemorrhagic fever virus (OHFV); the required vaccination coverage in endemic areas is 80–95% of the population[4] [63–65].

Viruses, especially RNA-containing viruses, are characterized by high natural variability, which, as a rule, surpasses the production capability of creating effective vaccines. The public health agenda gives a central place to development of universal vaccines of broad-spectrum antiviral effect targeting conserved viral proteins or their universal (conserved) domains or to use of viral epitopes eliciting a conserved cellular immune response in the recipient macroorganism. Such vaccines are expected to close a medical gap in case of emergence of new dangerous variants (genotypes) of viruses posing

[2]The Decree of the Ministry of Health of the Russian Federation, No. 1122n, issued on 06.12.2021, On Approval of the National Schedule for Preventive Immunization, the Schedule for Preventive Vaccination for Epidemic Reasons and the Procedure for Preventive Vaccination.

[3]Addendum No. 2 to the Decree of the Ministry of Health of the Russian Federation, No. 1122n, issued on 06.12.2021, On Approval of the National Schedule for Preventive Immunization, the Schedule for Preventive Vaccination for Epidemic Reasons and the Procedure for Preventive Vaccination.

[4]Prevention of tick-borne viral encephalitis. Sanitary and Epidemiologic Rules, SP 3.1.3.2352-08.

threat to people, such as avian influenza viruses, novel coronaviruses, poxviruses, Crimean-Congo hemorrhagic fever viruses (CCHFV), Ebola viruses, and others. Although such vaccines are still not available, the science has come close to their development; throughout the world, scientist are conducting active research in this area, for example, in using monoclonal antibodies in creating universal vaccines.

At present, chemotherapy is refocusing on creating new-type drugs targeting the factors in the host cell, which are essential for virus replication, rather than the virus. This approach differs from the classical "magic bullet" concept focused on the selective hitting of the target infectious agent, which was offered by the famous German scientist Paul Ehrlich in 1907 when he was working on targeted medicines for treatment of syphilis [66]. This new approach has been gaining pace for the last 15 years; it is based on the knowledge of molecular mechanisms involved in interaction of viruses with target cells and on knowledge of the molecular basis of the pathogenesis of viral diseases [67–70]. In the recent years, the process of building core knowledge of molecular nature has been picking up speed with new technologies brought into virology by proteomics, genomics, kinomics and genome editing [68, 71]. As opposed to drugs (the viral "magic bullet") targeting the virus, the agent of the cellular pathogenetic type will have broad spectrum antiviral activity and prevent the pathogen from developing drug resistance to the pathogenetic medication directed at the cell target. It is incredibly unlikely that pathogens will develop resistance to cellular target drugs, which can occur only in chronic cases having long-term drug therapy and only for categories of specific cell-directed drugs. Cell-directed medications will not only inhibit virus replication, but also will make it possible to inhibit or block the key factors in the pathogenesis of the viral disease, which contribute significantly to its severity; thus, they will help achieve high binary (antiviral and pathogenetic) treatment effect and prevent complicated disease forms. The first candidate agents of this type of cell-directed drugs have been developed recently and are being assessed through clinical trials. Such pilot products include antibodies – CCR5 receptor antagonists on the HIV-1 model [72, 73]; cyclosporine, which can inhibit the nuclear export of influenza virus RNA [74]; anti-claudin-1 and anti-occludin antibodies, which can inhibit the hepatitis C virus [75, 76]; imino sugars impairing the activity of cellular glycosidases and leading to abnormal glycosylation of viral proteins demonstrated their effectiveness against HIV viruses [77]; inhibitors of cellular heat shock protein (HSP70) demonstrated their effectiveness against SARS-CoV-2, Ebola and CCHF viruses [70]; inhibitors of the biosynthesis of cellular nucleosides, such as the inhibitor of the enzyme dihydroorotate dehydrogenase [78]; inhibitors of cellular proteases participating in activation of enveloped viruses showed high effectiveness against influenza viruses and coronaviruses [69, 79–81]. The development and improvement of the delivery routes for this category will make it possible to create a reliable stockpile of effective broad-spectrum antiviral drugs.

Hepatitis B (Hepadnaviridae: *Orthohepadnavirus*) and C (Flaviviridae: *Hepacivirus*)

Parenterally transmitted viral hepatitis B and C have a devastating impact on public health and economies. Russian virologists made a significant contribution to development of programs on diagnosis, prevention and treatment of viral hepatitis: Vitaly Aleksandrovich Ananiev (1921–2003), Efim Aleksandrovich Paktoris (1920–1994), Elena Severianovna Ketiladze (1919–1991), Mikhail Surenovich Balayan (1933–2000), Mikhail Ivanovich Mikhailov, Yevgeny Ivanovich Samokhvalov and many others.

The use of genetically engineered vaccines against hepatitis B caused by the hepatitis B virus (Hepadnaviridae: *Orthohepadnavirus*) gives an illustrative example of high effectiveness of vaccination. According to official data, the total number of people having chronic hepatitis B virus infection (HBsAg carriers) in Russia ranges from 1 to 3 million [82, 83]. The currently used drugs include nucleoside analogs such as lamivudine, which selectively inhibits the activity of the viral DNA polymerase. However, the virus develops resistance to its effect. Worldwide, around 100 thousand people die each year from fulminant hepatitis B, around 500 thousand – from acute infection, around 700 thousand – from cirrhosis and around 300 thousand – from hepatocellular carcinoma. Vaccination against hepatitis B also prevents hepatitis D coinfection [82, 84].

In June 1996, the Ministry of Health of Russia and the State Sanitary Epidemiological Surveillance Service issued joint decree No. 226179 "On Preventive Vaccination Against Hepatitis B", and the vaccination was included in the National Immunization Schedule. Mandatory vaccination was required for all infants to be vaccinated in three doses at 0–1–6 months, for all adolescents aged 13–14 years, and for all healthcare workers. In Russia, there is a wide variety of genetically engineered vaccines from Russian and international manufacturers. All of them are safe and highly effective. 95–97% of the vaccinated individuals develop protective concentrations of antibodies (> 10 mIU/ml) three months after administration of the last dose of the vaccination series. A certain problem is posed by pre-S and S gene escape mutants evading the effect of antibodies [83, 85]. Yet, hepatitis B is a vaccine preventable disease.

Note that the family Hepadnaviridae is composed of two genera – *Avihepadnavirus* (duck hepatitis B viruses, crane hepatitis B viruses) and *Orthohepadnavirus*, which, in addition to the human hepatitis B virus (HBV), includes woodchuck hepatitis viruses (WHV), arctic squirrel hepatitis viruses (ASHV), ground squirrel hepatitis viruses (GSHV), woolly monkey hepatitis B viruses (WMHBV) [86].

Hepatitis C caused by the hepatitis C virus (Flaviviridae: *Hepacivirus*) falls into the category of socially significant infectious viral diseases. An estimated 150–170 million people are infected with the virus world-

wide, including around 2 million people in Russia [87]. High incidence rates, high frequency of chronic forms w2ith subsequent cirrhosis and hepatocellular carcinoma, absence of vaccines, genetic diversity, difficulty and low effectiveness of treatment, expensive antiviral drugs clearly demonstrate the urgency of its research [82, 87–89]. At least, 9 genotypes have been identified; the divergence between them can reach 15–25%: 1 (1a, 1b, 1c), 2 (2a, 2b, 2k), 3 (3a, 3c, 3d, 3e, 3f), 4 (4a, 4b, 4c, 4d), 5 (5a), 6 (6a, 6b), 7 (7a, 7ab, 7cd), 8, (8a), 9 (9a) [87, 90]. The Institute of Virology conducted countrywide research on spread of genotypes of the hepatitis C virus (the silent killer), having identified the dominance of the most pathogenic genotype 1b [91] and having described the previously unknown genotype 2k [92].

Human immunodeficiency virus (Retroviridae: *Lentivirus*)

Starting from the second half of the 1980s, a number of virological groups immediately responded the global HIV infection pandemic: Viktor Mikhailovich Zhdanov, Otar Georgievich Andzhaparidze (1920–1996), Vadim Valentinovich Pokrovsky, Marina Ridovna Bobkova, Leonid Viktorovich Uryvaev, Alla Grigorievna Bukrinskaya, Mansur Magomedovich Garaev and many other researchers. A valuable contribution to the research was made by the team organized by Lev Stepanovich Sandakhchiev (1933–2000) who opened a large virological center – Vector – near Novosibirsk.

Two years after the first disease case was reported in the United States in 1981, the virus (HIV-1, human immunodeficiency virus, Retroviridae: *Lentivirus*) isolated by the Nobel prize laureate Luc Montagnier caused the pandemic slowly, but steadily spreading throughout the world. According to the molecular and genetic studies, the first human encounters with the virus in Africa date back to the 1920s–1930s and occurred at least three times. In Russia, the subtype A variant has been dominating since the beginning of the epidemic in 1996, though subtype B variants and variants of other subtypes as well as A/B and A/C recombinants have also been detected [93, 94]. The infection prevalence increased by 50% from 2001 to 2010. The molecular monitoring of circulating genetic variants of the virus, which is conducted in Russia, helps make decisions on medications for treatment [93]. Using combination of the existing (> 30) antiretroviral agents (entry inhibitors, nucleoside and nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, integrase inhibitors, protease inhibitors) help significantly extend life expectancy in infected people [95]. New approaches address eradication and functional cure (stem cell transplantation, gene therapy, etc.). HIV infection is another example of pandemic spread resulting from the transmission of the virus from animals to humans. Sooty mangabeys and other species of monkeys, except for chimpanzees, can be infected without clinical signs of immunodeficiency and are a wildlife reservoir of this group of retroviruses.

Viral diseases of domestic animals

Outstanding achievements were made by Russian virologists studying viral diseases of domestic animals (Vasily Nikolaevich Syurin, Mikhail Ivanovich Gulyukin, Taras Ivanovich Aliper, Alexey Dmitrievich Zaberezhny, Alexey Mikhailovich Gulyukin and many others). Among the most pressing problems, the central place is taken by African swine fever [96, 97], pestiviruses [98] and other viruses (more than 150) having veterinary significance. In addition to African swine fever (ASF, Asfarviridae: *Asfivirus*) and classical swine fever (CSF, Flaviviridae: *Pestivirus*), the most serious swine diseases include viral gastroenteritis caused by coronaviruses (Coronaviridae), reoviruses (Reoviridae) and others (more than 20 viruses in total). The most dangerous bovine diseases are foot-and-mouth disease (the etiological agent belongs to the family Picornaviridae), bluetongue disease (caused by the reovirus), rinderpest or cattle plague (Paramyxoviridae), enzootic bovine leukosis (Retroviridae), rhinotracheitis (Herpesviridae), bovine viral diarrhea (Flaviviridae) – more than 10 virus species. Life-threatening diseases of horses are African horse sickness (Reoviridae), Eastern and Western equine encephalitis (Togaviridae), equine infectious anemia (Retroviridae), equine arteritis (Arteriviridae), rhinopneumonia (Herpesviridae) – more than 24 in total. Canine distemper (Paramyxoviridae) and others – more than 12 in total – pose a threat to dogs and cats. Domestic fowl can be infected by more than 25 viruses from 12 families. Fish in aquaculture can be infected by viruses of at least three different families (Birnaviridae, Rhabdoviridae, Orthomyxoviridae). Bees can be infected by six known pathogenic viruses from the families Iflaviridae and Dicistroviridae.

Influenza and ARVI viruses

In the 1930s–1940s, the Soviet Union scientists started extensive research on influenza viruses, including influenza A viruses (Orthomyxoviridae: *Alphainfluenzavirus: Alphainfluenzavirus influenzae;* subtypes A(H1N1), A(H1N1pdm09), A(H3N2)) and B (Orthomyxoviridae: *Betainfluezavirus: Betainfluenzavirus influenzae*). The group of viruses – pathogens of acute respiratory diseases – included many other RNA-containing viruses: coronaviruses (Coronaviridae: *Alphacoronavirus*), paramyxoviruses (Paramyxoviridae: *Orthorubulavirus* – parainfluenza viruses type 2 and type 4; *Respirovirus* – parainfluenza viruses type 1 and type 3; *Orthopneumovirus* – the human respiratory syncytial virus; *Metapneumovirus* –human metapneumovirus), a number of rhinoviruses (Picornaviridae: *Enterovirus*; more than 152 serotypes) and others. They also include a number of DNA-containing viruses: bocaviruses (Parvoviridae: *Bocaparvovirus*), adenoviruses (Adenoviridae: *Mastadenovirus*; seven species including 54 serotypes: HAdV-A (12, 18, 31), HAdV-B (37, 11, 14, 16, 21, 34, 35, 50), HAdV-C (1, 2, 5, 6), HAdV-D (8-10, 13, 15, 17, 19, 20, 22-30, 32, 33, 36-39, 42-49, 51, 53, 54), HAdV-E (4), HAdV-A (40, 41), HAdV-G (52)). Thus, the seasonal variety of pathogens of acute respiratory viral infections (ARVI) consists of multiple co-circulating viruses (more than 200 genetic groups

from 6 families and 10 genera), which are very similar by their clinical presentation. They can be differentiated only using laboratory diagnostic methods, primarily, RT-PCR (reverse transcription polymerase chain reaction). In 2019, WHO launched the Global Influenza Strategy for 2019–2030 aimed at protecting people from the threat of influenza by improving epidemiological surveillance and preventing future pandemics. A priority attention is given to studies exploring the patterns of circulation of influenza viruses and their characteristics, variability and susceptibility mechanisms, minimization of risks associated with severe disease forms, development of new diagnostic testing systems and therapeutic agents. In Russia, these objectives are implemented through the system of countrywide centers supervised by the Research Institute of Influenza of the Health Ministry of Russia in St. Petersburg and the Center of Influenza Ecology and Epidemiology (CIEE) of the Ivanovsky Institute of Virology of Gamaleya NRCEM, together with regional departments and hygiene and epidemiology centers of Rospotrebnadzor in the European part of Russia, in the Urals, Siberia and the Far East.

A significant contribution to the studying of fundamental properties of viruses of influenza and other ARVI as well as to the development of diagnostic techniques and prevention methods was made by many Russian scientists: V.M. Zhdanov, V.D. Smorodintsev, V.D. Solovyov, A.S. Gorbunova, L.Ya. Zakstelskaya, R.S. Dreizin; and during the recent years – N.V. Kaverin, G.A. Galegov, F.I. Ershov, O.I. Kiselev, S.S. Yamnikova, M.Yu. Schelkanov, L.V. Kolobukhina, E.I. Burtseva and many others [99–104].

The family Orthomyxoviridae includes six genera, three of which – A, B, and C – are transmitted through respiratory routes and are responsible for annual seasonal epidemic outbreaks among people. Viruses of the genera *Thogotovirus* and *Quaranjavirus*, representatives of which were isolated in Russia, are transmitted to susceptible vertebrates and humans by bites of hard and soft ticks. Viruses of the genus *Isavirus* causes diseases among fish.

Influenza A viruses are especially dangerous. They circulate widely in the biosphere, especially among birds (18 known subtypes); the recent findings prove their occurrence in the ocean plankton. Thus, influenza A is zooanthroponosis characterized by ubiquitous spread. The population gene pool of these viruses has been forming for millions of years, probably, since the Cretaceous Period of the Mesozoic Era, through cross-population interactions between viruses and birds [17]. The segmented genome creates conditions for recombination of genes when two and more viruses replicate concurrently in the same organism. The resulting reassortants having high variability can have different biological and antigenic properties, providing most favorable conditions for thriving of the population in the population gene pool and for further panzootics and pandemics [17].

Natural foci of influenza A viruses can be found in many countries, including Russia. Our studies conducted in Northern Eurasia demonstrated that 15 out of 18 known influenza A viruses circulate among birds. The detected viruses include subtype H5, which is responsible for the severe panzootic among domestic poultry in 2003 [105]. Hundreds of millions of birds died or were destroyed. There were disease and death cases among people. In April 2005, during the spring migration along the Dzungar migration pathway, the virus came to Kazakhstan and Western Siberia, causing epizootics among domestic poultry across Russia and then in other countries. In April 2008, another genetic cluster of the virus was brought by migratory birds to the Primorye Territory and then headed northwards. Thus, two genetic clusters of influenza A(H5N1) virus circulate in Northern Eurasia. The death rate from virus A(H5N1) reaches 53% [106]. A total of 864 cases of influenza A(H5N1) human infection have been reported worldwide from 18 countries, including Southeast Asia, Egypt. The virus continues to circulate in natural biocenoses in Russia. From 2014 to present, a total of 79 human cases of avian influenza A(H5N6) virus infection have been reported, with the death rate reaching 43% [106]. Since 2013, a total of 1,568 human cases (the death rate reaching 39%) of avian influenza A(H7N9) virus infection have been reported. The virus emerged from reassortment of avian influenza viruses. It was brought to Russia by wild migratory birds during their spring migration and was spread through natural foci of infection. Later, during the autumn migration, the virus was brought from the Asian tundra to the Pacific coast of America; then 2-3 years after, along migration pathways, it was transmitted to the central and eastern part of the continent. Since 2015 to date, a total of 74 cases of human infection with avian influenza A(H3N8) and A(H7N4) have been reported, with the death rate of 2.7%. Human infections with avian influenza viruses most often occurred after close contact with infected birds. Although no cases of the avian influenza virus being transmitted from human to human have been reported, the possibility of such transmission cannot be excluded. Vaccine candidate strains must be developed and tested in advance to be used during future influenza pandemics. To date, bioengineers have constructed around 20 vaccinal strains for all known genetic clades of the H5 virus and other zoonotic influenza viruses [107]. Although the availability of these strains cannot prevent the disaster, it will help minimize the consequences.

Low-virulent strains usually circulate among wild birds. However, when they find their way into the populations of domestic poultry, these strains become high-virulent, mostly due to substitution of glutamine for lysine at position 627 of PB2 protein [108].

Amino acid residues constituting the receptor-binding site (RBS) are different for human, swine and bird receptors. The influenza A receptor is represented by two main types of covalent bonding of the terminal neuraminic acid residue to the previous monosaccharide of sialoglycans: α-2,6 for hemagglutinin (HA) RBS of epidemic strains and α-2,3 for HA RBS of avian virus strains [100, 109].

The annual mortality burden of influenza epidemics ranges from 200,000 to 500,000 deaths. Influenza affects from 5 to 10% of population, while the death rates reach 0.01–0.02%. Novel pandemic variants claim the

lives of millions of people. During the Spanish influenza pandemic in 1918–1919, the A(H1N1) virus killed around 100 million people, with the death rate reaching 0.5%. All influenza A viruses affecting mammals originated in birds. Considering that new pandemic variants may emerge in the foreseeable future, the circulation of the influenza virus should be monitored worldwide.

Since the beginning of its spread, the novel pandemic A(H1N1pdm09) virus, which is the recombinant virus circulating among humans, birds and pigs, has been characterized by a mixed type of α-2,6- and α-2,3-specificity and higher virulence compared to seasonal influenza A(H1N1) [110]. Shortly after the pandemic in Russia in 2009, we isolated strains from fatal cases with primary viral pneumonia, which carried amino acid substitutions of aspartic acid (D) with glycine (G) or asparagine (N) at the receptor-binding site of hemagglutinin HA1, thus causing the substitution of receptor specificity to epithelial cells of the respiratory tract for α-2,3 and the subsequent entry of the virus into the lower respiratory tract – alveoli and bronchioles – resulting in rapid development of fatal pneumonia [110, 111]. The similar findings were reported by researchers from other countries [112–114]. The transmission of such mutants from human to human has not been identified so far. Among the patients with detected mutants the death rate reached 60% [101]. The further experimental studies performed on ferrets demonstrated the possibility of this scenario, thus raising concerns about catastrophic consequences regarding the number of affected people and the economic impact [115, 116]. The above data show that influenza must be assigned to zooanthroponoses.

The synthesis of antiviral agents – a long (can take up to twenty years) and costly (billions of dollars) process is a key priority in the fight against influenza. Quite promising results have been shown by the antiviral drug Baloxavir Marboxil developed by Roche in 2018; it blocks the virus replication at the early stage by inhibiting the endonuclease of the polymerase complex [117]. It should be added to the stockpile of therapeutic agents available in the event of a pandemic. Rimantadine (an inhibitor of the ion-channel activity of the M2 integral membrane protein), which was commonly used in 1966–2010 and was synthetized by Russian specialists (G.A. Galegov, S.A. Giller, Ya.Yu. Polis, M.Yu. Lidak, M.K. Indulen, A.A. Smorodintsev, V.I. Ilenko, etc.), went out of action after the virus population became resistant to it due to amino acid substitutions in the M2 protein – S31N as well as A30V and V27A. Researchers are studying the ways to overcome resistance to adamantane derivatives [118]. Currently, the early treatment options for influenza include the neuraminidase inhibitor introduced in 1999, which prevents the release of the virus from the surface of an infected cell; oseltamivir (Tamiflu), zanamivir (Relenza) and peramivir. The above antivirals are also associated with occasional resistance due to amino acid substitutions H274Y in treatment with oseltamivir and Q136K – in treatment with zanamivir. The risk of resistance is constantly monitored at molecular and genetic levels [111, 119].

Three independent cases of emergence of novel human zooanthroponotic coronaviruses (Coronaviridae: *Betacoronavirus*) having an epidemic and pandemic potential have been reported since the early 2000s [120, 121]. The first epidemic outbreak of severe acute respiratory syndrome (SARS) infection caused by the novel SARS-CoV coronavirus (the subgenus *Sarbecovirus*) occurred in China in autumn of 2002 [122]. Over two years, a total of more than 8,000 cases and 774 deaths were reported (the fatality rate ranges from 4% to 11%). The second emergence of a novel pathogenic human coronavirus is associated with the epidemic outbreak of Middle East respiratory syndrome (MERS), which was reported in Saudi Arabia in autumn 2012. The virus that caused the MERS outbreak (MERS-CoV) belongs to the subgenus *Merbecovirus* [123]. By 2020, imported sporadic cases and epidemic outbreaks affecting dozens of people had been reported in 27 countries. The virus is responsible for more than 2.5 thousand cases and around 900 deaths. People are generally infected with MERS-CoV during their contact with camels who act as intermediate hosts for the virus [123]. The third outbreak caused by SARS-CoV-2 and rapidly expanded to a pandemic occurred in Wuhan, Hubei Province in China, in December 2019 [124]. According to the WHO data, by September 1, 2022, a total of 600,366,479 cases of SARS-CoV-2 and 6,460,493 deaths (the total mortality was estimated at 1.1%) had been reported worldwide. Russia reported 19,771,113 cases and 384,787 deaths (the total mortality was estimated at 1.9%).

The emergence of the SARS-CoV-2 virus and the resulting pandemic demonstrated the importance of monitoring of zoonotic viruses in natural reservoirs before they cross the species (taxa) barrier and spill over into human population. Horseshoe bats (*Rhinolophus* spp.) are the main wildlife reservoir of SARS-like coronaviruses; they are common in Asia, Europe and North Africa. The geographic range of horseshoe bats also covers southern regions of Russia, including North Caucasus and Crimea [125]. In Southeast Asia (including China), SARS-like viruses were detected in 23 different species of horseshoe bats [126]. Bat viruses, which were most closely related to SARS-CoV-2, were detected in some species of horseshoe bats in the Yunnan Province in China as well as in Thailand and Laos [127–130]. The large-scale studies conducted in Russia also resulted in detecting two new species of SARS-like coronaviruses, which were called Khosta-1 (as they were first found in Khosta-1 Cave) and Khosta-2 and circulated in populations of horseshoe bats on the northern coast of the Black Sea (the subtropical region in the Krasnodar Territory) [131]. Khosta-1 and Khosta-2 represent an individual clade (together with the viruses, which were earlier found in Bulgaria (strain BtCoV/BM48-31/2008) and Kenya (strain BtKY72)). Khosta-1 and Khosta-2 have the similarity ranging from 60 to 96% by different proteins with SARS-CoV and SARS-CoV-2 [131].

The spike (S) glycoprotein mediates virus entry into a host cell and is a primary determinant of virus tropism. It has a special receptor-binding domain (RBD) [132].

SARS-CoV and SARS-CoV-2 use the angiotensin-converting enzyme 2 (ACE2) as a cell receptor [133]. Most of the known bat viruses are not able to bind to ACE2 of humans or other animals, and their receptor remains unknown [134]. However, some Asian strains of bat viruses, though having significant differences with SARS-CoV-2 in the RBD sequence, are able to bind to the ACE2-receptor and use it for entry into a cell [128, 135–138]. In Laos, scientists discovered strains, which had the RBD sequence almost identical to that of SARS-CoV-2; one of them – BANAL-52 has only two amino acid substitutions and binds to the human ACE2-receptor almost as effectively as SARS-CoV-2 [130]. The structure of the receptor-binding motif of the S protein of Khosta-1 and Khosta-2 viruses bears a resemblance to that of SARS-CoV and SARS-CoV-2. *In vitro* tests have demonstrated the ability of Khosta-1 and Khosta-2 viruses to bind to the bat ACE2-receptor and use it to enter the cell; the Khosta-2 virus effectively binds to the human ACE2-receptor. The obtained results, together with the findings obtained in studies of other bat SARS-like viruses, show that the ability to bind to the human ACE-receptor is developed naturally in wildlife reservoirs in different genetic lineages and is an ancient evolutionary property of the group of coronaviruses. Evolutionary processes (antigenic drift, recombinations and genome rearrangements), which result in emergence of novel, potentially pathogenic variants of coronaviruses, are taking place in all parts of their range.

The additional extensive open translation frames – the so-called ambipolar genes – detected in the genome of influenza viruses and coronaviruses can be seen as an important discovery of the recent years [139–142]. It is a new type of viral genes, which have all the functional elements typical of expression of these genetic frames as translation genes [139, 142, 143]: AUG start codons (or the alternative CUG codon), translation stop codons [144], canonic Kozak sequences (Kozak consensus [145]), presence of typical ribosome landing pads (IRES – internal ribosome entry site [146]). The distinctive feature of the discovered genes is their ambipolar localization in the virus genome: positive-polar in the influenza virus (having the negative-polar genome) [147] and negative-polar in coronaviruses (having the positive-polar genome) [142, 148, 149]. The translation products of these genes in infected cells have not been identified yet; however, there are data supporting the development of a cellular immune response to protein products of ambipolar genes or to their specific domains in the body infected with the influenza virus, thus being indicative of the expression of these genes during the life cycle of viruses in the host [150–152]. If the expression of proteins – products of ambipolar genes in the viral infectious process is proven, changes must be made in the classification of families of orthomyxoviruses and coronaviruses and their (or their genera) assignment to virus families with the ambipolar genome strategy [142]. At present, 4 genera – phleboviruses, tospoviruses, arenaviruses and bunyaviruses – are assigned to such ambipolar viruses [153].

Arboviruses

The exceptional contribution to the development of virology was made by scientists studying arboviruses. Arboviruses represent an ecological group of zoonotic viruses transmitted through biological transmission to susceptible vertebrates by blood-sucking arthropods – hard (Ixodidae, 6 subfamilies and 14 genera) and soft (Argasidae, 5 genera) ticks and insects: mosquitoes (Diptera, Culicidae), sand flies (Psychodidae: *Phlebotomus*), midges (Diptera, Heleidae).

The first studies on arboviruses were performed at the end of the 19th century, when the Cuban entomologist C. Finlay and members of the United States Army Yellow Fever Commission headed by W. Reed proved the viral nature and the transmission of yellow fever virus by mosquito *Aedes aegypti* [10]. The term arthropod-borne (transmitted by arthropods) was introduced in 1942. In 1963, the International Sub-Committee on Nomenclature of Viruses recommended the term arbovirus for usage. There are more than 500 known arboviruses; more than 100 of them can cause diseases in humans and animals, including life-threatening diseases: epidemic outbreaks of hemorrhagic fever and encephalitis. In a number of cases, sudden epidemics of arbovirus infection affected the fighting capacity of the army and military operations.

In the Soviet Union, studies of arboviruses started in the early 1930s when army doctor-neuropathologist A. Panov, together with his colleagues A. Shapoval and D. Krasnov, described seasonal epidemic encephalitis with high death rates in the Far East. They defined the disease as “spring-summer encephalitis” and assumed that it was caused by the unknown virus. They detected a certain similarity between the infection and the “autumn-summer encephalitis” (Japanese encephalitis (JE) and St. Louis) known at that time; they also assumed that it could be a toxic form of influenza [154]. However, the etiology of the disease and its transmission routes remained unknown. To study the new infection, the People’s Commissariat of Public Health organized a number of field expeditions in 1937–1940. The expedition teams included specialists from different scientific organizations: virologists (L. Zilber, A. Smorodintsev, M. Chumakov, E. Levkovich, A. Sheboldaeva, A. Shubladze), bacteriologists (V. Solovyov, N. Ryzhkov), parasitologists (Ye. Pavlovsky, A. Gutsevich, B. Pomerantsev, A. Monchadsky, A. Skrynnik), clinicians (A. Panov, A. Shapoval, Z. Finkel) and others. During the summer period in 1937, the members of expeditions isolated around 30 strains of the new virus from blood, cerebrospinal fluid and autopsy material [155]. Several strains were also isolated from ticks *Ixodes persulcatus*, whose capability of transmitting the virus by bites was proven experimentally. One of the isolated strains (Sofjin) was used for experimental infection in macaques who developed clinical symptoms of encephalitis, which were similar to those observed in humans [156–159]. Thus, the etiological agent of spring-summer encephalitis, which is presently known as TBE, was isolated and studied. The TBE virus (TBEV) was the first arbovirus discovered by Soviet virologists.

Different aspects of TBE ecology, epidemiology and pathogenesis were extensively studied during the subsequent years. The first TBE vaccine was developed using brain tissue of mice infected with the Sofjin strain. During the further research, it was found that TBEV was also common in the European part of the Soviet Union and European countries, where it was mainly transmitted by ticks *I. ricinus*. The present-day classification assigns TBEV to the species *Tick-borne encephalitis virus* (Flaviviridae*: Flavivirus*). During the expeditions, several strains of the JE virus also belonging to the genus *Flavivirus*, but transmitted by mosquitoes, were isolated from patients in the Far East in 1938 during the Battle of Lake Khasan (the Changkufeng Incident). It was the first proof of JE virus circulation in the Soviet Union [160, 161]. However, after the outbreak in 1938, no JE cases were reported in the Soviet Union in the subsequent years.

The identification of TBEV as an etiological agent of spring-summer encephalitis propelled studies of the similar infections throughout the Soviet Union. In later years, a few large virological centers started operating under the umbrella of the Academy of Medical Sciences of the USSR: the Institute of Virology (1944), the Institute of Poliomyelitis and Viral Encephalitis (1950) as well as virological laboratories at medical institutes and plague control stations. Scientists from these centers took an active part in studies of different aspects of arboviruses circulating in the country. The extensive research on TBE is being conducted at present [162].

Many participants of the first field expeditions became famous virologists and founded their own schools of virology. The most outstanding researcher among them is Mikhail Petrovich Chumakov who was appointed the director of the Institute of Virology (1950–1954) and later the director of the Institute of Poliomyelitis and Viral Encephalitis, which was founded at his initiative (1955–1972). M.P. Chumakov organized multiple expeditions looking for etiological agents and studying natural and focal (primarily arboviral) infections. Among the arboviruses identified by him, pathogens of tick-borne hemorrhagic fevers – OHF and CCHF – are of special importance.

In the early 1940s, several rural areas of the Omsk Region (Southwest Siberia) reported an outbreak of the disease defined by local healthcare experts as "atypical tularemia", "anicteric leptospirosis", "Omsk spring-summer fever". The viral etiology of the disease named Omsk hemorrhagic fever (OHF) was identified by the group of specialists from the Omsk Medical Institute and virologists – members of the field expedition led by M.P. Chumakov in 1947 [163]. They isolated more than 40 strains of the virus from the blood of patients; the virus was called the OHF virus (OHFV). Several strains were also isolated from ticks *D. reticulatus* collected in the endemic regions [164]. The ecology, epidemiology and pathogenesis of OHFV were thoroughly studied in the subsequent years. The present-day classification assigns OHFV to the species *Omsk hemorrhagic fever virus*, the genus *Flavivirus* (Flaviviridae); it is included in the TBEV antigenic complex.

In June 1944, rural areas in the north of the Crimean Peninsula were hit by an outbreak of fever with hemorrhagic manifestations (acute infectious capillary toxicosis). A total of more than 200 cases were reported. The etiology of the disease called Crimean hemorrhagic fever (CHF) was identified by researchers – members of the field expedition led by M.P. Chumakov. It was assumed that the infection was transmitted by ticks *Hyalomma marginatum* (formerly, *H. plumbeum*), which are very common and numerous in the region of the outbreak. The viral etiology and zoonotic nature of the infection were identified by infecting volunteers with the blood collected from patients and the suspension prepared from ticks *H. marginatum* collected from hares. The infective material was filtered through fine-pore porcelain filters. The first strains of the CCHF were isolated from a patient in Uzbekistan (the Hoja strain) and from the serum collected from a patient as well as from nymphs *H. marginatum* in the Astrakhan Region (the Drozdov strain) by researchers from the Institute of Poliomyelitis and Viral Encephalitis (A.Butenko) in 1963–1967 [165, 166]. Later, it was found that the CHF virus was identical to the Congo virus isolated from patients with hemorrhagic fever in Zaire (Congo, Africa), and it received its present-day name – CCHFV [167]. In later years, different aspects of ecology, epidemiology, pathogenesis and clinical presentation of CCHF were thoroughly studied at the Institute of Virology, the Institute of Poliomyelitis and Viral Encephalitis, the State Research Center of Virology and Biotechnology Vector (Novosibirsk) and at other research centers of the Soviet Union [15]. The CCHF virus is one of the typical representatives of nairoviruses and belongs to the species *Crimean-Congo hemorrhagic fever virus*, the genus *Orthonairovirus*, the family Nairoviridae. No specific therapeutic strategies for CCHF have been developed yet, though ribavirin has proved to have some efficacy [168].

During spring and summer in 1962, M. Chumakov, jointly with E. Libkova from the Institute of Virology in Bratislava (Slovakia, former Czechoslovakia), did the research on the outbreak of fever (Kemerovo fever) in the Kemerovo Region (Western Siberia). The novel virus called the Kemerovo virus was isolated from blood of patients and from ticks *I. persulcatus,* which were collected in the region hit by the outbreak [169, 170]. Antigenically similar to the Kemerovo virus, the Tribec and Lipovnik viruses were later isolated from *I. ricinus* ticks in Czechoslovakia [171, 172]. Based on the virion morphology, the viruses were assigned to the genus *Orbivirus*, the family *Reoviridae*.

From 1930 to 1969, arboviruses were mainly studied as etiological agents of emerging human infections. Studies of arthropod vectors and vertebrate hosts in natural foci of major human infections frequently resulted in isolation of other arboviruses. For example, A. Butenko (the Institute of Poliomyelitis and Viral Encephalitis) was the first in the Soviet Union to isolate strains of the West Nile virus (Flaviviridae: *Flavivirus*) and Dhori virus (Orthomyxoviridae: *Thogotovirus*) from ticks *Hyalomma marginatum* during his exploration of CCHF natural foci in the Astrakhan Region in 1964. By the end of the 1960s, a total

of seven arboviruses had been identified or described in the Soviet Union: TBE and JE, CCHF and OHF, West Nile, Dhori and Kemerovo viruses. It was the beginning of the systemic ecological approach based on the concept of population interactions between species of viruses, arthropod vectors and vertebrate hosts and the environment. The task allotted to virologists was to create a system of research on natural foci of pathogens causing zoonotic infections, including arboviral infections.

The most important vertebrates – wildlife reservoirs for arboviruses are birds (Aves), rodents (Rodentia) and bats (Chiroptera). More than 200 known arboviruses are ecologically associated with birds. In some cases, birds remain the main vertebrate hosts, and in other cases, they serve as an effective amplifier for the virus. The role of birds in the circulation of arboviruses depends on several factors; most important of them are the large number and high density of populations at breeding sites (for aquatic and semi-aquatic birds), resting and wintering sites; seasonal migrations with transcontinental transportation of viruses and transmitters (ticks), burrow nesting [173]. Addressing the problem, several centers were opened in the Soviet Union to study zoonotic viruses associated with birds, including the All-Union Ornithology Committee with the coordination council on bird migration and medical ornithology and the All-Union Center for Virus Ecology and Epidemiological Protection of Civil Population and the Army. The All-Union Ornithology Committee operated at the site of the Institute of Biology of the Biological Department of the Academy of Sciences of the USSR (director V.D. Ilyichev) and the Institute of Virology of the Academy of Medical Sciences of the USSR (director D.K. Lvov). The Russian Center for Virus Ecology was opened at the Ivanovsky Institute of Virology, having an extensive network of support centers in all regions of the Soviet Union[5]. These two entities developed a joint research program and held conferences twice a year, discussing plans and research results. This system was similar to the American Epidemic Intelligence Service program sponsored by the Centers of Disease Control and Prevention (CDC) [174, 175].

The theoretical framework for monitoring different ecosystems incorporated methods of molecular ecology. The methodological approach involved longitudinal exploration of the Soviet Union and some bordering countries, including collection of field data and their subsequent laboratory analysis. The territory of Northern Eurasia covering more than 15 million square kilometers was studied. Probes passed through landscape zones of the Arctic, Subarctic (tundra), boreal forest, deciduous forests, steppes and deserts in 18 physical and geographical countries with unique ecosystems. Hundreds of virus strains were isolated and studied, including the previously unknown species. Researchers identified the etiological role of the isolated viruses in human pathology, describes previously unknown infections, assessed the potential risk of emergence of epidemic situations in different landscape zones of the Soviet Union, prepared the forecast for the geographic range of some types of emerging infections.

The regional support centers were opened almost in all regions of the Soviet Union; they were directed by energetic professional who promptly organized research teams, bringing together virologists, zoologists, and arachno-entomologists, who had required expertise in field and laboratory research. Their efforts were rewarded: Most of the leading research officers defended doctoral dissertations and their team members successfully defended their candidate dissertations, among them were I. Vinograd (Lviv, Ukraine), I. Voinov (Minsk, Belarus), P. Skofertsa (Kishinev, Moldavia), F. Karas (Bishkek, Kirgizstan), T. Pak, M. Kostyukov (Dushanbe, Tajikistan), S. Karimov (Alma-Ata, Kazakhstan), N. Mirzoeva (Baku, Azerbaijan), V. Zakaryan (Erevan, Armenia), M. Kurbanov (Ashkhabad, Turkmenistan), A. Meliev (Tashkent, Uzbekistan), V. Zlobin (Irkutsk), F. Busygin (Omsk), G. Leonova (Vladivostok), A. Timofeeva (Yuzhno-Sakhalinsk) and others.

Soviet scientists evaluated the biological background like it was done by specialists measuring the radiation background levels. Such evaluation included continuous routine studies focused on assessment of potential risks of emergence of any natural or human-caused epidemic situations and on mitigation of their consequences. The systemic studies of zoonotic viruses began in 1969 when the research program was adopted. In 1984, the program was given the national-level status and was supervised by the newly founded Russian Center for Virus Ecology and Especially Dangerous and Understudied Infections, which was opened at the Ivanovsky Institute of Virology (Director D.K. Lvov) [176]. The central goal of the program was to study the diversity and circulation of zoonotic viruses as well as to identify their threat to the biosafety of the country as pathogens of emerging and re-emerging infections. The program also focused on exploration of their ecology and evolutionary processes taking place in natural reservoirs. Field studies were conducted by employees of the All-Union Center of Virus Ecology in cooperation with local organizations and support centers. A specially designated section of the program deal with arboviruses circulating in polar latitudes of Northern Eurasia [177, 178]. One of the core sub-programs was focused on studies of ecology of influenza viruses in natural biomes, including subtypes A(H5N1) and A(H1N1pdm09) [161].

The results of the large-scale work were impressive: Scientists isolated virus strains ubiquitous in tundra, boreal forests, and deciduous forests and transmitted by mosquitoes, including viruses of the California encephalitis (the species *California encephalitis orthobunyavirus*) group and Batai virus group (the species *Bunyamwera orthobunyavirus*) the genus *Orthobunyavirus*, the family Peribunyaviridae [179]. California encephalitis viruses are associated with sum-

[5]Organization of ecological and epidemiological monitoring in the Russian Federation to provide epidemiological protection of the population and the army: Guidelines. Moscow: Ministry of Health of the Russian Federation, Federal Department of Medical, Biological and Extreme Problems, Research Institute of Virology, 1993.

mer cases of meningitis and meningoencephalitis. For the first time ever, the scientist were able to study the circulation of Sindbis viruses (SINV) causing Karelian fever and Getah viruses (GETV) belonging to the genus *Alphavirus*, the family Togaviridae in the Soviet Union, Finland and Sweden, having shown their role in human and animal pathology [180].

The system "ticks *Ixodes (Ceratixes) uriae* – colonial seabirds" was one of the most important targets of the ecological and virological studies conducted in the polar regions. In 1969–1974, hundreds of strains were isolated from ticks *Ix. uriae* collected in seabird colonies on the coast of the Sea of Okhotsk, the Bering Sea and the Barents Sea. Scientists collected almost 7 thousand ticks (representing all metamorphosis stages – larvae, nymphs, adults) from 1 m^2 of the surface nesting site and isolated up to 100 strains of seven different viruses. The research findings confirmed the circumpolar distribution of natural foci in the Northern and Southern Hemispheres. Most of the isolated strains were classified as previously unknown bunyaviruses, flaviviruses and orbiviruses, often based only on the virion morphology, as their antigenic relationships with other viruses had not been identified at that time. They included such newly discovered bunyaviruses as the Sakhalin virus (SAKHV) and the Paramushir virus (PRV), which later were included in the species *Sakhalin orthonairovirus*, the genus *Orthonairovirus*, the family Nairoviridae [181]. Several new viruses (the Terpeniya Bay, Komandory, Rukutama) were described and later classified as the species *Uukuniemi phlebovirus*, the genus *Phlebovirus*, the family Phenuiviridae [182].

For the first time, a new flavivirus – the Tyuleniy virus (TYUV) and the related Kama virus from Tatarstan were isolated to become later typical representatives of seabird tick-borne flaviviruses (the genus *Flavivirus,* the family Flaviviridae) [183]. The circulation and ecological characteristics of the Okhotsky virus (OKHV) and the Aniva virus (ANIV), two newly discovered and described viruses of the species *Great Island virus* (the genus *Orbivirus*, the family *Reoviridae*) were thoroughly studied [184].

Multiple new viruses were discovered during studies conducted in Central Asia and South Caucasus. The Issyk-Kul virus (ISKV), the etiological agent Issyk-Kul fever, which is associated with bats (Vespertionidae) and their soft ticks was identified and described in detail [185]. Issyk-Kul fever is a serious disease; the recovery process lasts for two months. The emerging Tamdy virus (TAMV) and Burana virus (BURV), which cause sporadic cases of fever, were isolated from *Hyalomma* spp. ticks collected from goats and cows in desert biocenoses [186]. Several novel viruses (Artashat, Chim, Geran) were first isolated from soft ticks collected in rodent burrows. Based on the results of the morphological studies, they were assigned to unclassified bunyaviruses. In recent publications, the above viruses are classified as different species belonging to the genus *Orthonairovirus*, the family Nairoviridae [187]. The Karshi virus (KARV), which is related to the Royal Farm virus (Afghanistan), was first isolated from soft ticks. It is closely related to TBEV and causes sporadic cases of fever in people. A novel flavivirus – Sokuluk virus (SOKV) was first isolated in Central Asia; it is ecologically associated with bats *Vespertilio pipistrellus* and is related to the Entebbe bat virus from Africa [188]. The novel Tyulek virus (TYKV) was isolated in Kirghizia from soft ticks collected burrow nests of birds; later, it was assigned to the genus *Qaranjavirus*, the family Orthomyxoviridae. All the above listed viruses, including many more viruses, were isolated and identified during the implementation of the research program.

The most fundamental results obtained during the research were summarized in the special Atlas of Distribution of Natural Focal Viral Infection Pathogens in the Russian Federation, which was published in 2001, and in a number of other books [161, 189]. The final stage of the research involved identification of genetic characteristics and classification of isolated viruses using advanced methods of genome analysis, including next-generation sequencing (NGS). As a result, new species and genera of zoonotic viruses were identified. To date, a total of more than 80 species of zoonotic viruses belonging to 12 different families circulating in Northern Eurasia have been identified.

The research program was implemented in cooperation with international scientists, primarily, with virologists from the United States and WHO representatives. For example, during different times, D.K. Lvov was a consultant at the American Committee on Arboviruses, a member of the international committee for research on arboviruses in polar latitudes, a coordinator representing the Soviet Union in studies of influenza ecology in the joint project between the United States and the Soviet Union, a WHO expert and the chairperson of the Committee on Medical Sciences and Public Health of the Pacific Science Association.

The program implementation was so successful and significant that many participants received State Science and Technology Awards in 1999. The list of nominees included scientists from the Ivanovsky Institute of Virology: A. Butenko (diagnosis and identification of isolated strains), S. Gaidamovich (implementation of new methods of studying biological properties of viruses), V. Gromashevsky (isolation of viruses and their identification), P. Deryabin (building the collection of strains and viruses), S. Klimenko (the electron microscopic study of viruses), L. Kolobukhina (research on clinical presentation of infection), S. Lvov (studies of viruses in polar latitudes, field research), D.K. Lvov (the program director, ornithology studies, field research). Three scientists (D.K. Lvov, S. Klimenko, V. Zlobin) were elected members of the Academy of Medical Sciences of the USSR (presently, the department of the Russian Academy of Sciences).

The research under the program continued in the subsequent years. At the beginning of this century, the West Nile fever (WNF) epidemiological situation worsened drastically in the south of Russia. High mortality rates (affecting 10% of the cases) were reported. Comprehensive six-year-long studies were conducted in the Astrakhan and Volgograd Regions and in Kalmykia; as a result, the scientists were able to describe the circulation patterns of the pathogen (the West Nile virus (WNV)), its

molecular and genetic characteristics, mechanisms of development of stable natural foci involving birds, domestic animals, mosquitoes and ticks [190]. Recently, WNV has significantly expanded its geographical range, spreading to the Voronezh, Saratov, Rostov Regions and Krasnodar Territory. In 2022, cases of WNF were reported in Moscow. Simultaneously with the events in the south of Russia, seemingly, out of nowhere, the WNF outbreak with high death rates occurred in New York City (the United States) and the surrounding areas in 1999. Within a short time, it spread throughout America via main migration pathways of migratory birds: Atlantic, Mississippian, central and Pacific. The West Nile virus first evolved in Africa. The virus could not have been brought to the American continent through natural routes in the last 80 million years since the break-up of Pangea in the Cretaceous Period of the Mesozoic Era. The virus could be brought by infected mosquitoes in holds of ships sailing from the Mediterranean Sea or the Black Sea ports. These outbreaks show how careless or criminal human actions can activate powerful natural mechanisms, thus creating dangerous epidemic situations. The phylogenetic analysis of genomes showed that the epidemic strains from Russia and the United States were related. However, they differed significantly from the strains isolated previously when there were no epidemic outbreaks. Therefore, the epidemic situations may have been associated with the changed genetic properties of the virus population during the evolution of the virus in the wildlife reservoir. Arboviral and other zoonotic viral infections, which have social, military and medical significance, are actively studied throughout the world.

Arboviral infections (zoonoses, zooanthroponoses) are an archetype of other human infections having come a long way over the last 10 thousand years from zoonoses to zooanthroponoses and anthroponoses [17]. The theory of natural focality of infections, which was developed by Ye.N. Pavlovsky, had a strong influence on studies of arboviral infections and other zoonotic diseases [191]. Researchers studying arboviruses should be proficient not only in virology, but also in arachnoentomology, zoology, climatology and other related sciences. Russian and foreign researchers have put their health and life at risk, working in natural foci of infections, which have not been described yet. The names of outstanding researchers, who worked in all continents, are etched into the history of arbovirus studies: in the United States (C. Calisher, J. Casals, R. Chamberlain, W. Downs, S. Halsteed, D. Gubler, N. Karabatsos, J. Le Duc, T. Monath, F. Murphy, W. Reeves, R. Shope, W. Sudia, R. Taylor, R. Tesh, M.Turrel, T. Work, etc.), Canada (H. Artsob, C. Chastel, etc.), Brazil (O. Causey, O. Lopes, F. Pinheiro, Travassos da Rosa, etc.), Venezuela (J. Navarro, etc.), Egypt (M. Darwish, etc.), South Africa (R. Kokernot, B. McIntosh, K. Smithburn, R. Swanepoel, etc.), France (P. Brech, C. Hannoun, etc.), United Kingdom (D. Bishop, C. Ross, J. Woodale, H. Reid, J. Porterfield, etc.), Norway (T. Traavik, etc.), Czechoslovakia (V. Bardos, M. Gresikova, H. Libikova, J. Rehacek, etc.), Yugoslavia (V. Vesenjak-Hirjan, A. Gligic, etc.), Finland (M. Brummer-Korvenkontio, N. Oker-Blom, etc.), India (K. Pavri, C. Dandawate, K. Banerjee, etc.), South Korea (H. Lee, S. Yun, etc.), Malaysia (S. Lam, etc.), China (B. Chen, H. Huang, Y.-X. Li, Hi Liu, etc.), Japan (A. Hotta, A.Igarashi, N. Kitaoka, K. Morita, etc.), Australia (Y. Aaskov, R. Doherty, J. Mackenzie, Y. Marshall, etc.), New Zealand (J. Miles, etc.). Annual international conferences provided prompt information about activity of natural and zooanthroponic foci, while mutual cooperation made it easier to exchange virus strains for expansion of national collections. Epidemic of dengue fever and O'nyong-nyong fever affecting millions of people, dozens or sometimes hundreds of thousands of people infected with yellow fever, Venezuelan, Western, Eastern, Japanese, tick-borne, Murray Valley, California, Rocio, St. Louis encephalitis, Rift Valley, sandfly, West Nile fevers, CCHF, etc. – to name a few arboviral infections dangerous both for humans and domestic animals [192]. Infections can be difficult to diagnose due to the huge genetic diversity of pathogens. The absence of specific therapeutic agents and even preventive vaccines explains the concerns of WHO, scientists and healthcare workers about the problem that also has veterinary, military, medical, and environmental significance [192]. The main biological risk facing biological species, including humans, is associated with the encounter with the pathogen that the above species had never been in contact with due to environmental distancing ("strangers' encounter").

Modern approaches of genome analysis in virology

New technologies of genome analysis (massive parallel sequencing, next generation sequencing – NGS), which have been developed since the end of the 20th century, are used actively in different fields of virology. Based on the recent data, the currently known viruses account for less than 0.01% of the global virodiversity [193, 194]. To some extent, the responsibility for this lies with the classical virological methods, which can be applied only to the viruses that can be isolated using a laboratory model (cell cultures or laboratory animals). If a virus cannot be isolated from the used model, it remaines invisible for the researcher. This explains the existence of a relatively small number of the presently known viruses (a total of around 10 thousand species). In the last years, the NGS technology has offered the possibility to describe genetically viruses by analyzing the virome and transcriptome of their host, thus taking the understanding of the diversity of the viral world, its evolution and the role of viruses in biosphere to the next level [195]. The analysis of viromes of different species of animals, arthropods and environmental samples helped detect and identify hundreds and thousands of emerging viruses, including those that are evolutionary related to the known human pathogens or represent new divergent clades [196, 197]. Recognizing the efficiency of NGS as a method of genome analysis, the virome analysis is seen as a promising method of monitoring of zoonotic infections in wildlife reservoirs, thus making it possible to identify the entire range of circulating

viruses and their genetic variants. NGS-based effective approaches have been developed for diagnosis of infections. During the ongoing pandemic of COVID-19, the whole-genome sequencing of SARS-CoV-2 strains is performed in the real-time mode, providing the possibility to use molecular epidemiology methods and timely detect the emergence and spread of new variants of the virus. In the meantime, despite its undisputable advantages, this approach cannot be used for identification of biological and antigenic properties of the detected viruses. Therefore, classical virological methods based on the isolation of strains using a laboratory model remain the backbone of modern virology.

Guides to virology

Addressing the problem of lack of information, two Russian-language guides were published in 2008 and 2013, summarizing information about viruses and viral human infections (more than 150) and animal infections (more than 150). The role of viruses in biosphere, ecology of viruses, their structural components, genome strategies, interaction with cells were analyzed in detail. The description was given to families of viruses that are pathogenic for humans and animals. The detailed description was given to virus-induced immunity, chemotherapy for viral infections, laboratory diagnostics and preventive vaccination, virological, molecular and genetic methods [198].

The role of the Ivanovsky Institute of Virology of the Academy of Medical Sciences of the USSR in development of Russian and global virology

The role of the Ivanovsky Institute of Virology in the development of Russian virology can hardly be overestimated. The Institute was given life by Decree No. 797 issued by the Council of People's Commissars on June 30, 1944 – "On Establishment of the Academy of Medical Sciences of the USSR (AMS)", the Institute of Virology being its part. The Institute was named after D.I. Ivanovsky, the founder of virology, following Decree No. 4344 issued by the Council of Ministers of the USSR on October 19, 1950. A student of D.I. Ivanovsky, E.I. Turevich, worked at the institute for 16 years, taking care of the consistency of research. Another scientist working during these years was V.L. Ryzhkov, an associate member of the Soviet Academy of Sciences (viral diseases of plants). The first director of the institute was professor Anatoly Timofeevich Kravchenko, who 6 years later became the chief research officer of a large virological center of the Ministry of Defense of the USSR. The first deputy director of research was academician Lev Aleksandrovich Zilber, who later organized a large virology department at the Gamaleya NRCEM of AMS. For a short time, the Institute of Virology was directed by academician Anatoly Aleksandrovich Smorodintsev, who later founded the Research Institute of Influenza in Leningrad. One of the first deputy directors of research was academician Valentin Dmitrievich Solovyov, who afterwards became the head of the virological department at the Institute of Epidemiology and Microbiology. During the five-year directorship of academician Mikhail Petrovich Chumakov, the Institute of Virology significantly improved its cooperation with regional scientific and research centers, thus promoting large-scale field research and establishing the system of training of specialists in virology. In 1955, M.P. Chumakov became the director of the Institute of Poliomyelitis and Viral Encephalitis (IPVE), which he founded, and which later was named after him. The next director of the Institute of Virology was academician Pavel Nikolaevich Kosyakov. The center for influenza was founded, combining 19 support centers across the country; later, it was transformed into a WHO center. From 1961 to 1987, the Institute of Virology was led by academician Viktor Mikhailovich Zhdanov, who turned the institute into a modern scientific center enjoying global reputation. The school of molecular virology was founded; 6 WHO centers were opened, focusing on influenza, arboviruses, virus ecology, herpes, viral hepatitis, AIDS. The first issues of the journal "Problems of Virology" were published. V.M. Zhdanov teamed up a number of laboratories to study HIV infection; the first strains were isolated and further used for creating Russian diagnostic testing systems and conducting fundamental studies. In cooperation with researchers from the Engelhardt Institute of Molecular Biology and the Central Institute of Epidemiology, Russian scientists developed a Russian anti-HIV drug – p-hosphazide (Nikavir). The developers received the State Science and Technology Award (professor Georgy Artemievich Galegov) [99]. Long-term cooperation was established with virologists from more than 30 countries in America, Europe, Asia, Australia. Training of specialists has always been a priority at the Institute of Virology. Many future directors of academic institutions studied there as postgraduate students: Academician Boris Fyodorovich Semyonov became the director of the Mechnikov Research Institute of Vaccines and Sera, academician Otar Georgievich Andzhaparidze was the director of the Institute of Virus Preparations, academician Soslan Grigorievich Dzagurov was the director of the Tarasevich Institute for Standardization and Testing of Medical and Biological Products, academician Pyotr Grigorievich Sergiev was the director of the Martsinovsky Institute of Medical Parasitology and Tropical Medicine, while supervising the research on measles. Academician Oganes Vagarshakovich Baroyan was the academic secretary at the Institute of Virology; then he was appointed the director of the Institute of Epidemiology and Microbiology. Thus, the Institute of Virology was an "incubator" of directors of research institutes across the country, giving top-priority attention to training personnel for research and healthcare centers by providing postgraduate courses, internship and joint research projects. Academician Dmitry Konstantinovich Lvov was the director of the Institute of Virology from 1987 to 2016; prior to that, he had worked as the deputy science director for 19 years. In 2016, the Institute of Virology ceased to exist as a freestanding entity and became a subdivision of Gamaleya NRCEM of the Ministry of Health of Russia.

Conclusion

130 years after D.I. Ivanovsky described the first pathogen of the viral infection, the Russian virology continues to stay at the forefront of many priority areas such as research on the origin and evolution of viral pathogens posing a national and global threat to biosafety of human population and environment. The smart combination of theoretical approaches to exploration of the virus evolution with innovative techniques used for studying molecular and genetic characteristics of viruses as well as the subsequent development of new-generation vaccines and antivirals will help significantly minimize the consequences of future pandemics. The risk that devastating epidemic situations can occur in the foreseeable future is very high. "Wisdom should reckon on the unforeseen" (Edgar Poe).

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