EDITORIAL CONCEPT

Formation of population gene pools of zoonotic viruses, potentially threatening biosafety

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The possible formation of population gene pools of zoonotic viruses with a respiratory route of transmission and a possibility of a pandemic at different stages of biosphere evolution is analyzed. Forming of Poxviruses (*Entomopoxvirinae*) gene pool could be the beginning of transformation from Plants to Arthropoda (Carbon – 375 million years ago) with further evolution connected with *Rodentia* (Pliocene – 75–70 million years ago) and further separation of genera (500–300 thousand years ago), and respiratory transmission (epidemics) between humans (10–2 thousand years BC). Smallpox comeback would be possible. Orthomyxoviruses relicts (genus *Isavirus*) were possibly connected with *Ichthya* (Silurian – 500–410 million years ago), and then close interaction with *Aves* (the Cretaceous, 125–110 million years ago) with the division of genera and respiratory transmission (epidemics) between humans (10–2 thousand BC). Next pandemic of influenza A could be catastrophic in terms of the number of victims and economic damage.
Coronaviruses formed a gene pool by interaction with *Amphibia* (subfamily *Letovirinae*) and then with *Chiroptera* in Tertiary (110–75 million years ago) with transformation to *Artiodactyla* (Eocene – 70–60 million years ago), and only 10–2 thousand years BC acquired the ability to a respiratory transmission and became *Alphaviruses*, a seasonal infection of humans. A similar situation is possible in the near future with SARS-CoV-2. Pandemics associated with zoonoses even more serious than COVID-19 are likely. Constant monitoring of populational gene pools of zoonotic viruses is necessary.

***Keywords**: evolution; populational gene pools; viral population; Poxviridae; Orthomyxoviridae; Coronaviridae; Aves, Rodentia; Chiroptera; phylogenetics.*

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Формирование популяционного генофонда потенциально угрожающих биобезопасности зоонозных вирусов

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Проведён анализ возможного формирования популяционного генофонда вирусов с респираторной передачей, способных к развитию пандемий, на различных этапах эволюции биосферы. Наземное формирование генофондов поксвирусов (подсемейство *Entomopoxvirinae*) могло начаться с их перехода с голосеменных растений на членистоногих (карбон, 375 млн лет назад) с дальнейшей эволюцией, связанной с грызунами в палеоцене (75–70 млн лет назад) и разделением на роды (300–500 тыс. лет назад) и респираторной передачей (эпидемии) среди людей (10–2 тыс. лет до н.э.). Возможен возврат натуральной оспы.

Реликты ортомиксовирусов (род *Isavirus*), возможно, были связаны с рыбами (*Ichthya*) (силур, 500–400 млн лет назад), а затем их эволюция была тесно связана с птицами (меловой период, 135–110 млн лет назад) с разделением на роды и респираторной передачей среди людей с эпидемическим распространением (10–2 тыс. лет до н.э.). Последующие пандемии гриппа А могут быть катастрофичными по числу жертв и экономическому ущербу.

Коронавирусы начали формировать генофонд, взаимодействуя с земноводными (подсемейство *Letovirinae*), но в основном с рукокрылыми (*Chiroptera*) в третичном периоде (110–85 млн лет назад), образуя также переход на парнопалых (эоцен, 70–60 млн лет назад) и лишь 10–2 тыс. лет до н.э. приобретя способность к респираторной передаче (в первую очередь, вероятно, представителями рода *Alphacoronavirus*), обособились в сезонную инфекцию людей. Подобная ситуация возможна в ближайшем будущем с SARS-CoV-2. Эпидемические катаклизмы, более серьезные, чем COVID-19, связанные с зоонозными вирусами, вероятно, возникнут и в будущем. Необходим постоянный мониторинг популяционных генофондов зоонозных вирусов.

Ключевые слова: *эволюция; популяционный генофонд; Poxiviridae; Orthomyxoviridae; Coronaviridae; птицы; грызуны; летучие мыши; филогенетика.*

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The COVID-19 epidemic that emerged in 2019 and developed into a pandemic has caused the need to return to the problem of emerging and reemerging infections. The birth of virology as a science and its development contributed the history of this problem [1]. Unexpected epidemic emergencies resulting from natural disasters or criminal actions pose a threat to national and global biosafety, since the fight at the stage of their emergence is difficult or impossible. Viruses infect everything living on earth, i.e. representatives of the kingdoms of Viruses (virophages), Archaea, Bacteria, Algae, Plants, Fungi, Protozoa, Animals, and Humans (**Table 1**). All human viral infections were originally zoonoses, the pathogens of which, as a result of epyvolution, overcame the interspecies (intertaxon) barrier and eventually began to circulate in the human population, turning into zooanthroponoses and anthroponoses. With the emergence of articulation in hominins *Homo sapiens* in the modern epoch of the Quaternary period of the Cenozoic era, it became possible to transmit viruses (e.g., smallpox, influenza, and a complex of seasonal respiratory viruses) by the respiratory route. However, this was preceded by evolutionary events in populations of viruses and their hosts, about 3.5 billion years in length, associated with the evolution of the environment. The most important stages were the emergence of prokaryotes in the Archean, eukaryotes in the Proterozoic, the origin of the main types of animals in the Cambrian, the emergence of fish in the Silurian, amphibians in the Devonian, reptiles in the Carboniferous-Jurassic (Paleozoic–Mesozoic), insectivorous mammals (*Insectivora*) and birds in the Cretaceous period of the Mesozoic Era, bats in the Tertiary period of the Cenozoic Era, rodents in the Paleocene, and eventoed animals in the Eocene (**Table 1**).

All these events preceded the emergence of man. The first primates appeared in the Paleocene Epoch and the remains of the first human ancestors (the *Pongidae* family) are attributed to the Oligocene. Hominids appeared in the Pliocene, and Pithecanthropus and other hominins (genus *Homo*) were established in the Pleistocene of the Quaternary period. The ancestors of *H. sapiens* began interacting with animal virus populations at the beginning of the modern period. And after the emergence of articulation in hominins, viruses capable of airborne transmission began to spread actively (**Table 1**). The domestication of animals, which took place 20–10 thousand years ago, significantly activated the transition of animal viruses to humans [2]. The evolution of viruses in natural ecosystems as a result of changes in their population gene pool creates a threat of the constant emergence of new genetic clusters.

Table 1. Scheme of stages of the evolution of biosphere and its possible influence on viral gene pools

Era	Period	Epoch	Age (mln years)	Background representatives of the biosphere and their predecessors	Known potential viruses (interaction consequences)
Archean			3500–2000	Prokaryotes: Archaea (*Archea*)	≥ 9 families (Myo-, Sipho- Ampulla- etc.)
Proterozoic			2000–1000	Prokaryotes: bacteria (*Bacteria*). Eukaryotes: protozoa (*Protozoa*); algae (*Algae*); fungi (*Fungi*); plants (*Plantae*). Invertebrates (marine) (*Invertebrata*)	≥ 12 families (Myo-, Podo-, Sipho- etc.) ≥ 6 families (Reo-, Pseudo-, Mini- etc.) ≥ 9 families (Phycodna-, Pseudo-, Endorna etc.) ≥ 14 families (Pseudo-, Endorna-, Partiti- etc.) ≥ 26 families (Gemini-, Reo-, Rhabdo- etc.) ≥ 25 families (Baculo-, Reo-, Meta-, Pox- etc.)
Paleozoic	Cambrian		1000–550	Arthropods marine (*Arthropoda*), trilobites The origin of most types of modern animals	Intertaxon transmission of viruses
	Ordovician		550–500	Molluscs, trilobites Lichens	The beginning of the transition of gymnosperms to land
	Silurian		500–410	Horsetails, fernsArachnids (marine) (*Arachnoidea*) Vertebrates: Pisces (*Ichthya)*	≥ 11 families (Orthomyxo-, Reo-, Rhabdo- etc.)
	Devonian		410–375	Amphibians (*Amphybia)*	≥ 4 families (Adeno-, Irido-, Alloherpes etc.)
	Carbon		375–325	Ferns, ploonsThe emergence of the class of reptiles (*Reptilia*), arthropod dominance (*Arthropoda*)	≥ 18 families (Pox-, Reo-, Rhabdo- etc.)
	Permian		325–240	Dominance of reptiles (*Reptilia*)	≥ 7 families (Adeno-, Irido-, Reo-, Parvo- etc.)
Mesozoic	Triassic		240–225	The flourishing of reptiles (*Reptilia*) Flowering plants (*Angiospermae*)	≥ 26 families (Reo-, Rhabdo-, Gemini- etc.)
	Jurassic		225–135	The flourishing of reptiles (*Reptilia*)	≥ 7 families (Adeno-, Irido-, Parvo-, Reo- etc.)
	Cretaceous		135–110	Class Mammals (*Mammalia*): Order Insectivores (*Insectivora*) Birds (*Aves*)	≥ 31 families (Herpes-, Adeno-, Reo- etc.) ≥ 20 families (Orthomyxo-, Adeno-, Reo- etc.)
Cenozoic	Tertiary		110–85	Order Bats (*Chiroptera*) The flourishing of birds and placental mammals	≥ 10 families (Corona-, Adeno-, Reo- etc.) Generation of gene pools Orthomyxo-, Corona-, Pox- etc.
	Paleogene	Paleocene	75–70	Order Rodents (*Rodentia*) **Order Primates (*Primates*)**	>23 families (Pox-, Hanta-, Reo-, Herpes- etc.) **≥ 26 families (Corona-, Pox-, Orthomyxo- etc.)**
		Eocene	70–60	Even-toed ungulates (*Artiodactyla*) Odd-toed ungulates (*Perissodactyla*) **Simians (*Anthropoidea*)**	≥ 24 families (Pox-, Orthomyxo-, Reo- etc.) ≥ 18 families (Pox-, Orthomyxo-, Reo- etc.)
		Oligocene	60–40	Old World monkeys (*Cercopithecidae*) **Apes (*Pongidae*)**	≥ 20 families (Adeno-, Pox-, Reo-, Picorna- etc.) **Accidental infection of individuals without epidemic consequences**
	Neogene	Miocene	40–25	Rodents (*Rodentia*): family Squirrels (*Sciuridae*) subfamily Ground squirrels (*Marmotinae*) family Hamsters (*Cricetidae*) subfamily Gerbils (*Gerbillinae*) suborder Mouse-like rodents (*Myomorpha*)	*Poxviridae* *Hepadnaviridae, Poxviridae* *Poxviridae* *Poxviridae* *Poxviridae, Hantaviridae, Herpesviridae*
		Pliocene	25–6	**Family Hominids (*Hominidae*)**	**Accidental infections of individuals**
	Quaternary	Pleistocene	5–1	**Sub-family Hominines (*Homininae*)** **Genus *Homo*: *H. pithecanthropus, H. sinanthropus* and other hominins**	**Bipedalism. Enhancing contacts with animals on the hunt**

Table 1 to be continued on page 246.

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Era	Period	Epoch	Age (mln years)	Background representatives of the biosphere and their predecessors	Known potential viruses (interaction consequences)
		Holocene	500–300 thousand	***H. heidelbergensis*, *H. neanderthalensis* and other representatives of *H. sapiens* ancestors**	**The beginning of interaction between populations of viruses and hominins.** *Poxviridae* — division into genera
			300–40 thousand	***H. sapiens* (formation of the population gene pool); acquisition of articulation; beginning of domestication (dogs)**	**Respiratory transmission of viruses (smallpox, influenza, coronaviruses and other infections)**
			10–2 thousand BC	**First civilizations; domestication of artiodactyls (sheep, goats, cattle, pigs), equids (horses), birds (ducks, geese, chickens, turkeys); settling rodents into housing**	**Interaction of population gene pools of *H. sapiens*, domestic animals and viruses; respiratory viruses epidemics; epizootics of viruses with alimentary transmission; the transition of zoonoses to zooanthroponoses and anthroponoses**
			2 thousand years BC – XIX century.	**Formation of civilizations and activation of contacts (migration of peoples, wars, trade, colonization, development of new territories)**	**An increase in the number of anthroponoses, the emergence of new and recurring infections**
			XXI century	**High population size and density Traffic flows, globalization. Large farms of farm animals**	**Pandemics and panzootics**

Note. *One of the existing schemes was used. Some discrepancies in chronology are not of fundamental importance in the framework of the problem under discussion.

These processes underlie the emergence of emerging and reemerging infections.

The process of interpopulation interaction of viruses and their hosts in changing environmental conditions, in other words, the ecology of viruses, determines the changes in the population gene pool, i.e. its evolution. Population is a unit of evolution. The study of the population gene pool and the direction of changes in it is critical for finding the causes of epizootics and epidemics [3]. How does the outburst of viral populations take place out of common ecological niches? Where do the populations persist in the period between epidemics? Why do the properties of the populations change? The answers to these questions are necessary to predict the occurrence of epidemic emergencies. Therefore, system research is required to reveal the principal laws that ensure the preservation of viruses in the biosphere, to identify the pathways of their evolutionary variability by molecular-genetic methods, to determine the principal laws of genetic material movement in viral populations and formation of their gene pool.

In the course of evolution, the most successful relationships, in terms of species preservation, are formed between viruses and hosts [3, 4], which most often correspond to the average level of virulence of the pathogen and susceptibility of the host. For example, the persistence of viruses in birds and bats ensures their dissemination over a vast territory during the period of seasonal migrations. Epidemics and epizootics are often just an episode in the existence of a viral population. They occur, for example, in the case of influenza A (H5N1) viruses moving from wild birds to domestic ones. Low-virulent strains circulating among wild birds as a result of a long-term (probably dozens of millions of years) mutual adaptation are transformed into highly virulent ones, in particular, as a result of the replacement of E627K in the PB2 protein [5].

Over the past 120 years, at least ten pandemics and panzootics have arisen and spread in the world, including Russia; they were caused by zoonotic viruses transmitted through airborne route (alimentary route in birds). Lethality among humans was within 0.1–50%, among poultry – 20–90%. The number of victims aounted to about 500 million people (**Table 2**), the economic damage exceeded hundreds of billions, perhaps trillions of dollars. In natural biomes, the same or genetically close pathogens circulate among rodents (smallpox virus – *Poxiviridae; Orthopoxvirus*), birds (influenza viruses – *Orthomyxoviridae; Alphainfluenzavirus*), and bats (coronaviruses – *Coronaviridae, Betacoronavirus;* subgenera *Merbecovirus* and *Sarbecovirus*).

The *Orthomyxoviridae* family may have begun to form (genus *Isavirus*) since the Silurian Period of the Paleozoic Era (more than 400 million years ago) due to the emergence of fish. In the Carboniferous (378–325 million years ago), with the emergence of terrestrial arthropods (*Arthropoda*), representatives of the genera *Thogotovirus* and *Quaranjavirus* could have appeared. In the Cretaceous Period of the Mesozoic Era (110–135 million years ago), the formation of the genus *Alphainfluenzavirus* became possible, the representatives of this genus are closely related to birds (**Table 1**).

Table 2. Modern ecological relations of viruses of respiratory complex

Viruses				Hosts (types, classes, orders)																						
				Arthropoda				*Vertebrata*																		
				Arachnids (*Arachnoidea*)	Insects (*Insecta*)			Reptiles (*Reptilia*)		Amphibians (*Amphybia*)			Mammals (*Mammalia*)													
													Primates (*Primates*)													
Family/subfamily/genome		Genus/subgenus		Ticks (*Acari*)	Dipterans (*Diptera*)	Beetles (*Coleoptera*)	Lpidopterans (*Lepidoptera*)	Snakes (*Serpentes*)	Crocodiles (*Crocodilia*)	Frogs (*Anura*)	Pisces (*Ichthya*)	Birds (*Aves*)	Human (*Homo*)	Monkeys (*Simia*)	Bats (*Chiroptera*)	Carnivores (*Carnivora*)	Odd-toed ungulates (*Perissodactyla*)	Even-toed ungulates (*Artiodactyla*)	Rodents (*Rodentia*)	Lagomorphs (*Lagomorpha*)	Pinnipeds (*Pinnipedia*)	Cetaceans (*Cetacea*)	Eulipotyphla (*Insectivora*)			
Poxviridae dsDNA, linear, 130–375 Kb	*Entomopoxvirinae*	*Alphapoxvirus*		–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
		Betapoxvirus		–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
		Gammapoxvirus		–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	Chordopoxvirinae	*Avipoxvirus*		–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–
		Capripoxvirus		–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–
		Cervipoxvirus		–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–
		Leporipoxvirus		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	+	–	–	–	–	–	–
		Molluscipoxvirus		–	–	–	–	–	–	–	–	–	+	+	–	–	+	–	–	–	–	–	–	–	–	–
		Orthopoxvirus		–	–	–	–	–	–	–	–	–	+	+	–	+	+	+	+	+	–	+	–	–	–	–
		Parapoxvirus		–	–	–	–	–	–	–	–	–	–	–	–	–	+	+	–	–	–	–	–	–	–	–
		Shipoxvirus		–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–
		Yatapoxvirus		–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–
		Not classified		–	–	–	–	–	+	–	–	–	–	+	–	–	–	–	+	–	–	+	+	–	–	–
Orthomyxoviridae ssRNA(–), segmented (6–8), 0,7–2,8 Kb each		*Quaranjavirus*		+	–	–	–	–	–	–	–	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–
		Thogotovirus		+	–	–	–	–	–	–	–	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–
		Influenzavirus C		–	–	–	–	–	–	–	–	?	+	–	–	–	–	–	–	–	–	–	–	–	–	–
		Influenzavirus B		–	–	–	–	–	–	–	–	?	+	–	–	–	–	–	–	–	–	–	–	–	–	–
		Influenzavirus A		–	–	–	–	–	–	–	–	+	+	+	+	+	+	+	+	–	+	+	–	–	–	–
		Isavirus		–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Coronaviridae ssRNA(+), linear, 26–32 Kb	*Letovirinae*	*Alphaletovirus*		–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	Orthocoronavirinae	*Alphacoronavirus*	*Colacovirus*	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–
			Decacovirus	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–
			Duvinacovirus	–	–	–	–	–	–	–	–	–	+	–	+	–	–	–	–	–	–	–	–	–	–	–
			Luchacovirus	–	–	–	–	–	–	–	–	–	–	–	?	–	–	–	+	–	–	–	–	–	–	–
			Minacovirus	–	–	–	–	–	–	–	–	–	–	–	?	+	–	–	–	–	–	–	–	–	–	–
			Minunacovirus	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–
			Myotacovirus	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–
			Nyctocovirus	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–

Table 2 to be continued on page 248.

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РЕДАКЦИОННАЯ КОНЦЕПЦИЯ

Viruses			Hosts (types, classes, orders)																				
			Arthropoda				*Vertebrata*																
			Arachnids (*Arachnoidea*)	Insects (*Insecta*)			Reptiles (*Reptilia*)		Amphibians (*Amphybia*)			Mammals (*Mammalia*)											
												Primates (*Primates*)											
Family/subfamily/genome	Genus/subgenus		Ticks (*Acari*)	Dipterans (*Diptera*)	Beetles (*Coleoptera*)	Lpidopterans (*Lepidoptera*)	Snakes (*Serpentes*)	Crocodiles (*Crocodilia*)	Frogs (*Anura*)	Pisces (*Ichthya*)	Birds (*Aves*)	Human (*Homo*)	Monkeys (*Simia*)	Bats (*Chiroptera*)	Carnivores (*Carnivora*)	Odd-toed ungulates (*Perissodactyla*)	Even-toed ungulates (*Artiodactyla*)	Rodents (*Rodentia*)	Lagomorphs (*Lagomorpha*)	Pinnipeds (*Pinnipedia*)	Cetaceans (*Cetacea*)	Eulipotyphla (*Insectivora*)
		Pedacocovirus	–	–	–	–	–	–	–	–	–	–	–	+	–	–	+	–	–	–	–	–
		Rhinacovirus	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–
		Setracovirus	–	–	–	–	–	–	–	–	–	+	–	+	–	–	–	–	–	–	–	–
		Tegacovirus	–	–	–	–	–	–	–	–	–	–	–	?	+	–	+	–	–	–	–	–
		Incertae sedis	–	–	–	–	–	–	–	–	–	–	–	?	–	–	–	–	+	–	–	–
	Betacoronavirus	*Embecovirus*	–	–	–	–	–	–	–	–	–	+	–	?	+	+	+	+	+	–	–	–
		Hibecovirus	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–
		*Merbecovirus**	–	–	–	–	–	–	–	–	–	+*	–	+	–	–	–	–	–	–	–	–
		Nobecovirus	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–
		*Sarbecovirus***										+**		+							–	–
	Deltacoronavirus	*Andecovirus*	–	–	–	–	–	–	–	–	+	?	–	–	–	–	–	–	–	–	–	–
		Buldecovirus	–	–	–	–	–	–	–	–	+	?	–	–	–	–	+	–	–	–	–	–
		Herdecovirus	–	–	–	–	–	–	–	–	+	?	–	–	–	–	–	–	–	–	–	–
		Moordecovirus	–	–	–	–	–	–	–	–	+	?	–	–	–	–	–	–	–	–	–	–
	Gammacoronavirus	*Cegacovirus*	–	–	–	–	–	–	–	–	–	?	–	–	–	–	–	–	–	–	+	–
		Igacovirus	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–
Adenoviridae dsDNA, linear, 26–48 Kb	5 genera		–	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	+
Parvoviridae ssDNA(+), linear, 4–6 Kb	2 subfamilies, 9 genera		–	+	+	–	+	–	–	–	+	+	+	–	+	+	+	+	+	+	–	–	–
*Picornaviridae**** ssRNA(+), linear, 7–9 Kb	12 genera		+	–	–	–	+	–	–	+	+	+	+	+	+	+	+	+	–	–	+	–	–
*Paramyxoviridae***** ssRNA(–), linear, 15–19 Kb	2 subfamilies, 7 genera		–	–	–	–	+	–	–	+	+	+	+	+	+	+	+	+	+	–	+	+	–

Note. *MERS-CoV. **SARS-CoV, SARS-CoV-2. ***The *Picornaviridae* family is included in the order *Picornavirales* along with the families *Dicistroviridae* (insect viruses), *Iflaviridae* (insect viruses), *Marnoviridae* (unicellular algae, phytoplankton viruses), *Secoviridae* (plant viruses), as well as *Cheravirus, Sadwavirus, Sequivirus, Torradovirus, Waikavirus* (plant viruses) [61, 62].**** The family *Paramyxoviridae* is a member of the order *Mononegavirales* along with the families *Bornaviridae* (viruses of birds, horses, humans), *Filoviridae* (viruses of bats, primates, humans), *Rhabdoviridae* (viruses of plants, arthropods, fish, birds, mammals, including humans) [63].

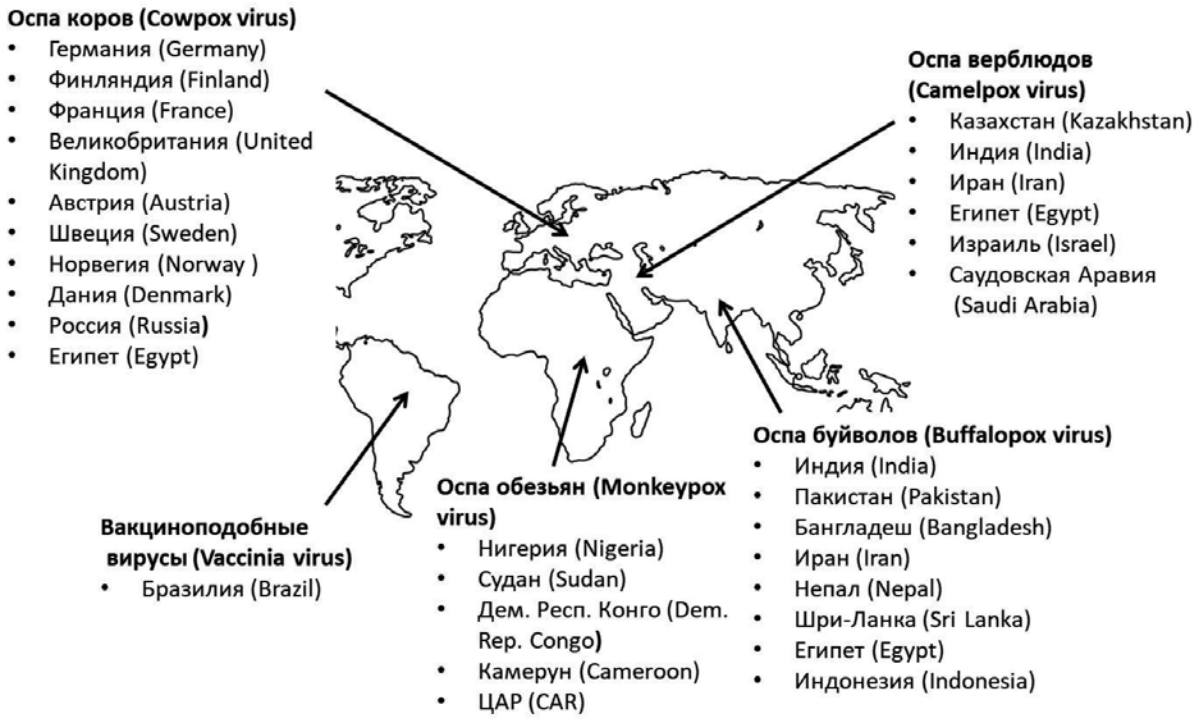

Fig. 1. Activation of foci of existing Orthopoxviruses in the world after the eradication of smallpox.

Poxviruses (subfamily *Entomopoxvirinae*) adapted to insects (*Insecta*) may have originated in the Carboniferous. Further evolution of poxviruses (subfamily *Chordopoxvirinae*) continued in rodent populations (*Rodentia*) in the Paleocene (75–70 million years ago) with further evolution in populations of even-toed animals (*Artiodactyla*) in the Eocene (70–60 million years ago). The final division of poxviruses into genera occurred in the modern epoch of the Quaternary Period about 500 thousand years ago (**Table 3**, **Fig. 1**) [6–9]. Rodents (*Rodentia*) remained the main natural hosts (**Table 2**). They serve as the main natural reservoir for orthopoxviruses. Natural centers are located on a huge territory from tropical deserts to subarctic tundra (**Fig. 1**) [9]. The reemergence of natural smallpox virus is theoretically possible, as it happened at least three times in the past [6–10]. According to American researchers, the use of the smallpox virus by terrorists is comparable to damage from the explosion of a hydrogen bomb [11]. The lethality in the case of smallpox disease reaches 40–60% of the number of victims in the case of airborne infection.

Obviously, such a course of evolution of zoonotic orthopoxviruses cannot be ruled out in the future, with a gradual transition from wild animals to domestic animals, and then to humans [8–10, 12]. The increasing frequency of monkeypox outbreaks among humans in Africa in recent years, including 2020, is alarming. Studies have shown that the natural reservoir of the virus is rodents. There are at least 4 species of squirrels (*Sciuridae: Rodentia*) in West and Central Africa, which have been diagnosed with asymptomatic infection. Thus, monkeypox is actually the smallpox of squirrels and other rodents [13-21]. In recent years, Brazil, India and Pakistan have reported outbreaks among domestic animals and people in contact with them caused by zoonotic smallpox viruses associated with rodents. We have isolated the Murman smallpox virus from the root vole *Microtus oeconomus* in the uninhabited Lovozero Massif of the Kola Peninsula [22]. Based on genome sequencing, eleven orthopoxviruses isolated in Africa, Asia and America were identified. According to the calculations of specialists from Novosibirsk-based «Vector» Federal Budgetary Institution of Science State Scientific Center of Virology and Biotechnology of the Russian Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing (Rospotrebnadzor) based on the analysis of the accumulation rate of mutations in the genome, the separation of poxviruses from the progenitor virus began about 500 thousand years ago. The calculations have shown that the types of camel smallpox and African barefoot gerbils (*Tatera*), which are evolutionarily close to the natural smallpox virus, emerged from a common ancestor about 4,000 years ago [6, 7, 23, 24]. It allows the possibility of the virus outburst into the human population against the background of almost absent collective immunity (**Fig. 2**) [9]. The consequences will be disastrous. It requires the development of the fourth generation smallpox vaccine and effective and safe chemotherapeutic agents.

Viruses with a high degree of genome variability are especially dangerous. These are, first of all, viruses of the *Orthomyxoviridae* family. Four genera of influenza viruses (*Alphainfluenzavirus, Betainfluenzavirus, Gammainfluenzavirus,* and *Deltainfluenzavirus*) are transmitted by the respiratory route and cause annual epidemics and pandemics

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РЕДАКЦИОННАЯ КОНЦЕПЦИЯ

Table 3. Viral pandemics (panzootics) of zoonotic origin with a respiratory (alimentary) infection (1900–2020)

Date range	Infection agent			Disease				Source of infection	
	family/subfamily	genus/subgenus	virus	name	location	lethality, %	number of deaths	natural reservoir	intermediate hosts
1900– 1977	*Poxviridae*	*Orthopoxvirus*	*Varicella major virus*	Smallpox	Hindustan, ubiquitously	40–50	300 million (in XX century)	Rodents	Buffaloes, monkeys
1918–1919	*Orthomyxoviridae*	*Alpha influenza virus*	A/H1N1	Spanish flu	USA, ubiquitously	0,5	100 million	Birds of the aquatic - near-aquatic complex	Poultry
1956–1958			A/H2N2	Asian flu	China, ubiquitously	0,02	> 4 million	-“-	-“-
1968 to present			A/H3N2	Hong Kong flu	China, ubiquitously	0,01	> 1 million	-“-	-“-
2009 to present			A/H1N1/pdm09	Pandemic flu	Mexico, USA, ubiquitously	0,1	> 5 million	-“-	-“-
2003 to present			A/H5N1	Avian flu *	China **	50	455	-“-	-“-
2013 to present			A/H7N9	Avian flu *	China	40	615	-“-	-“-
2014 г. to present			H5N6	Avian flu *	China	30	77	-“-	-“-
2012 to present	*Coronaviridae Coronavirinae*	*Betacoronavirus Merbecovirus*	MERS-Cov	Middle East respiratory syndrome-MERS-Cov	Saudi Arabia, United Arab Emirates	35	876	Bats	Camels
2002–2003		*Betacoronavirus Sarbecovirus*	SARS-Cov	Severe acute respiratory syndrome-SARS-Cov	China *	11	100 thousand	-“-	Civets and other animals ecologically associated with bats
2019 to present			SARS-Cov-2	COVID-19	China, ubiquitously	2,0–4,5	> 1 million	-“-	Pangolins and other animals ecologically associated with bats
Total							About 500 million		

Note. *Epidemic outbreaks. **Panzootics.

Flu kills 250–600 thousand people every year.

among humans, and epizootics and panzootics of wild and domestic animals, primarily, when transmitted through water and feed. Viruses of the *Thogotovirus* and *Quaranjavirus* genera, found in Russia as well, are transmitted to sensitive vertebrates and humans through the bites of ixodid and argas ticks. Viruses of the *Isavirus* genus infect fish (**Fig. 3**) [9].

Influenza A viruses are the most important part of the problem of novel infections. The segmented genome contains eight genes encoding viral proteins, which creates conditions for gene recombination in the event of simultaneous replication of two or more viruses in one organism. Emerging recombinants, providing a high degree of variability, can have different biological and antigenic properties, which helps them (if included in the population gene pool) overcome the host's protective cellular systems and, in some cases, provide the occurrence of panzootics and pandemics [25].

Influenza A viruses are widespread in the biosphere; according to the latest data, even ocean plankton contains them, but birds are their main natural reservoir. These population relationships have been firmly established since the Cretaceous Period of the Mesozoic Era (100-130 million years ago). Only 2–10 thousand years BC, with the emergence of the first civilizations, influenza A viruses, having changed the receptor affinity from α2-3 to α2-6, acquired the ability for airborne transmission among people with the occurrence of epidemics and later pandemics. There are orders of magnitude among more people on Earth today than it would be expected for populations of mammals of our size. These are ideal conditions for pandemics to occur. Natural centers of influenza viruses are still widespread. Our survey of the territory of Northern Eurasia revealed the circulation of 15 out of 18 known subtypes of Influenza A viruses among birds, including H5, which is associated with the severe epizootic that broke out in 2003 followed by the panzootic among birds (**Fig. 4**) [25]. Hundreds of millions of birds in Southeast Asia and Oceania died and were killed. People were infected and died (**table 3**) [26]. In April 2005, an epizootic outbreak among wild birds

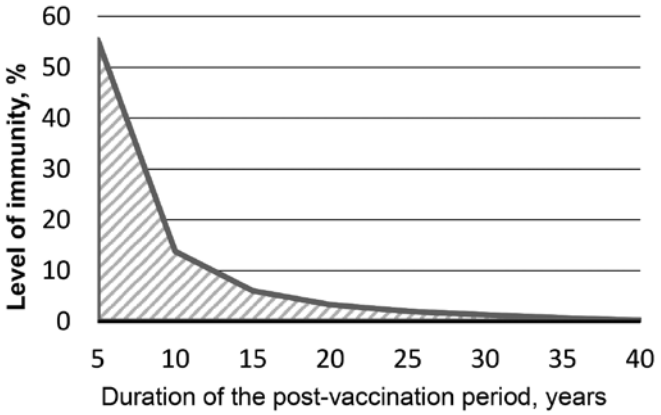

Fig. 2. Duration of smallpox post-vaccination immunity.

broke out on Qinghai Lake in the PRC, the northeastern part of the Tibetan Plateau. During the spring migration, the viral strains moved to the north along the Dzungarian Gate between the Tien Shan and Mongolian Altai, which links Southeast Asia with Central Asia and Western Siberia. West Siberian highly virulent strains HPAI form a fairly compact genetic Qinghai-Siberian group 2.2.

In early April 2008, the virus penetrated the territory of the southern Primorsky Territory with migrating birds and spread to the North. With the emergence of the Ussuriysk clade in Northern Eurasia, the following genetic clusters were formed: the Qinghai-Siberian cluster (2.2) – in the western sector, the Ussuriysk cluster (2.3.2) – in the eastern sector of Northern Eurasia (**Fig. 4**). The mortality rate caused by H5N1 avian influenza among humans is still very high in the world, namely 60%. This is higher than for smallpox. As of July 2020, 879 cases were detected worldwide among people in 16 countries of South-East Asia and in Egypt. The virus continues to circulate in natural biomes in Russia [27, 28].

The infection process begins with the attachment of the influenza virus to a cellular receptor – a derivative of sial-

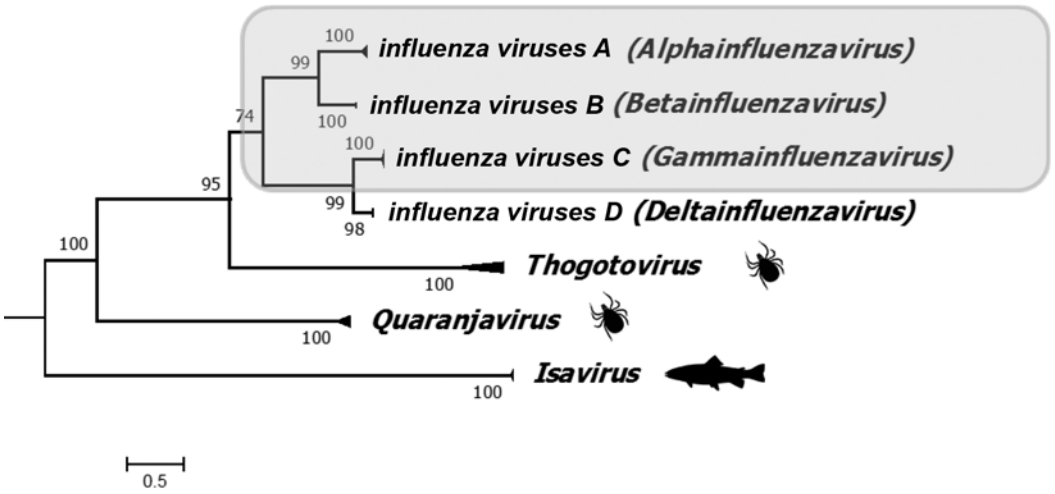

Fig. 3. Phylogenetic structure of the *Orthomyxoviridae* family.

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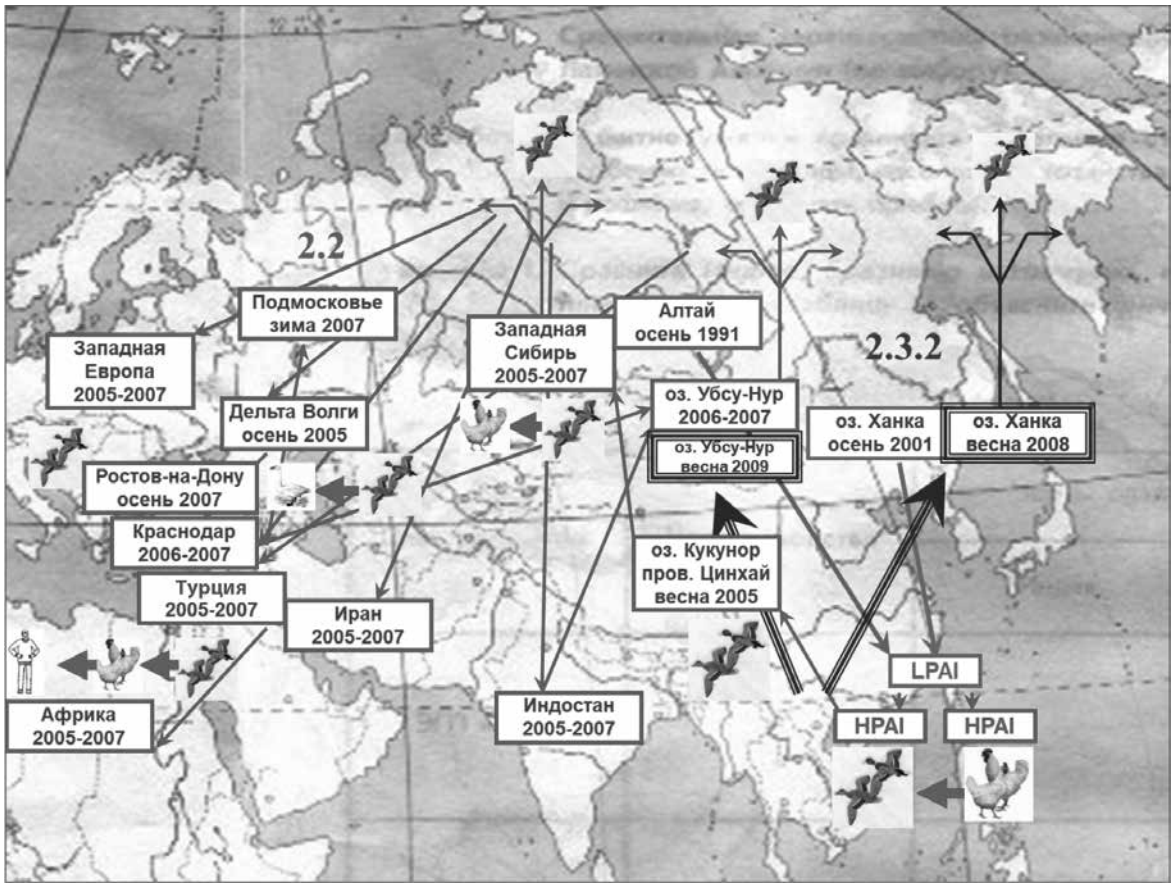

Fig. 4. Consequences of the penetration of a highly virulent A(H5N1) influenza virus into Northern Eurasia (spring 2005 – spring 2008).

ic acid attached to galactose or glucosamine by an α2-3- or α2-6-bond, which is recognized by influenza viruses, depending on the host. Human influenza viruses infect cells with α2-6-receptors located on the nasal mucosa. The number of these receptors gradually decreases in the following order: nasopharynx, trachea, bronchi, bronchioles. α2-3-receptors were found on bronchiolar and alveolar cells decreasing in number up the respiratory tract, and in birds – on intestinal epithelial cells [27]. The novel pandemic virus H1N1pdm09, which emerged on the border of Mexico and the United States, is a reassortant of two swine viruses of the American and Euro-Asian genotypes. The virus changed its receptor specificity from α2-3 to α2-6, gaining the possibility of reproduction in the upper respiratory tract, and thus it acquired the unique ability of influenza viruses to spread indefinitely with noticeable mortality among humans (**Table 3**).

The increase in virulence is particularly associated with a mutation in receptor-binding site 222 of hemagglutinin HA1 with the replacement of aspartic acid by glycine or asparagine. In this case, the virus changes its receptor specificity from α2-6 to α2-3 and acquires the ability to damage the lower respiratory tract, causing lethal pneumonia. We have carried out a genetic examination of over 100 materials from patients with lethal outcome. In all cases, death was caused by primary pneumonia. In 70% of cases, the sequencing revealed mutants of the pandemic virus in the lung tissue of deceased patients, who were not vaccinated and did not receive antiviral drugs at the early stages. However, the mutants lost the ability (α2-6-receptor affinity) for airborne transmission. If this ability persists (α2-3–α2-6), the consequences can be catastrophic, the experimentally possibility of such events has been proven [29, 30].

Since February 2013, i. e. at the beginning of the spring bird migration season, the human incidence was identified in China, etiologically associated with H7N9, another avian influenza A virus. As of mid-September 2019, 1,567 cases of human infection were laboratory – confirmed with 40% mortality, similar to smallpox. The virus appeared as a result of reassortment of influenza A viruses in wild birds. It was brought to the territory of Russia by wild birds with the formation of natural centers of infection. Then, the virus was delivered by migratory birds from the Asian tundra to the Pacific coast of America, and further, along the migration channels, it penetrated the central and eastern parts of the continent over the period of 2–3 years [9].

It is necessary to prepare candidate vaccine strains in advance for using them during future influenza pandemics. To date, bioengineers across the world have already designed about 20 vaccine strains for all known genetic clades of the H5 virus and other zoonotic influenza A viruses (**Table 4**) [31]. The main research was carried out in the

United States with significant contributions by Chinese and British researchers. Only one strain was obtained in the Russian Federation [32]. The availability of these strains will not prevent the disaster, but it will minimize the consequences.

Further development of antiviral chemotherapeutic agents with a new mechanism of action is requied as well. In particular, Baloxavir Marboxil developed by Roche in 2018 is very promising. This drug blocks viral replication at the early stage by inhibiting the endonuclease of the polymerase complex. The drug has already been registered in the United States, Japan and some other countries and is needed as a reserve.

We analyzed the situation with a virus from the *Betacoronavirus* genus (*Coronaviridae: Coronavirinae*) [33, 34]. The main natural reservoir of viruses of the *Coronavirinae* subfamily are bats (**Table 2**) [35–42]. Moreover, besides China, viruses similar to the epidemic ones were isolated from bats in Western Europe [43–45], in America [46, 47], and in Africa [48, 49].

Mutual adaptation of populations of bats and coronaviruses could have started in the Tertiary Period of the Cenozoic Era (110–85 million years ago) followed by the formation of the *Orthocoronavirinae* subfamily. The order *Chiroptera* (bats) includes at least 16 families, 170 genera and about 850 species; it ranks second in terms of the number of species after rodents. Bats are a very important natural reservoir for zoonotic viruses. A huge population gene pool was accumulated, allowing the representatives of this subfamily (*Coronavirinae*) to spread among birds and mammals, including Humans, Carnivores, Odd-toed and Even-toed mammals, Rodents, Double-toothed rodents, Insectivorous (**Table 2**). Representatives of the *Letovirinae* subfamily adapted to *Amphibia* may belong to relict species that could have started forming in the Devonian Period of the Paleozoic Era (about 400 million years ago) (**Tables 1** and **2**).

The SARS-CoV-2 pandemic that emerged in 2019 will be significantly reduced by joint efforts. But there is no reason for the disappearance of the pathogen that caused it. It is likely that SARS-CoV-2 with a reduced virulence will circulate in human populations for the foreseeable future as a seasonal respiratory virus along with coronaviruses belonging to the *Alphacoronavirus* genus (*Duvinacovirus* subgenus, HCoV) and other seasonal respiratory viruses: of the *Orthomyxoviridae* family (influenza viruses A/H1N1pdm2009, A/H3N2, B); of the *Paramyxoviridae* family (*Paramyxovirinae*), *Rubulavirus* genus

Table 4. Genetic clades of subtypes A(H5), A(H7), A(H9), and A(H1) of Influenza virus A

Genetic clade (subtype)		Host (birds)	Location	Availability of vaccine candidate
1.	H5N1	Wild and domestic	Eurasia, Africa	+
1.1.	H5N1	Domestic	Southeast Asia	+
1.1.2.	H5N1	Wild	Southeast Asia	+
2.1.1.	H5N1	Domestic	China	+
2.1.3.2.	H5N1	Domestic	Southeast Asia	+
2.1.3.2a	H5N1	Domestic	Southeast Asia	+
2.2.	H5N1	Wild, domestic	China, Russia, Eurasia, Africa	+
2.2.1.	H5N1	Domestic	Africa (Egypt), Asia (Turkey)	+
2.2.1.1.	H5N1	Domestic	Africa (Egypt)	+
2.2.1.2.	H5N1	Wild and domestic	Eurasia, Africa (Egypt)	+
2.3.2.1.	H5N1	Wild	China	+
2.3.2.1a	H5N1	Domestic	India, China, Nepal, Bangladesh, RF	+
2.3.1.1c	H5N1	Domestic	Southeast Asia, Africa (Cameroon)	+
2.3.2.1a	H5N1	Wild, domestic	Bangladesh*, India*, Nepal	+
2.3.2.1в			China	+
2.3.2.1c	H5N1	Domestic	Southeast Asia*	+
2.3.4.4h	H5N8	Wild and domestic	China*, Laos, Japan	+
2.3.4.2.	H5N8	Domestic	Bangladesh, China	+
2.3.4.4a	H5N8	Wild and domestic	Asia, Europe, Africa, America	+
2.3.4.4c	H5N2	Wild and domestic	China, South Korea, Vietnam, Japan, Philippines	+
2.3.4.4e	H5N2/N8	Domestic	Cambodia, China, Bulgaria*, Germany*,	–
2.3.4.4.	H5N5	Wild and domestic	Czech Republic, Georgia, Netherlands, Hungary*, RF, Montenegro	–
7.1.	H7N9	Domestic	Vietnam	+
7.2.	H7N9	Wild	China, Niderlands*	+
	H7N4	Domestic	China	–
	H9N2	Wild and domestic	Asia, Africa	+
	H1N2	Domestic (pigs)	USA*, Brazil*, Germany	

(HPIV-2,4), *Respirovirus* genus (HPIV-1,3 – human parainfluenza viruses), *Pneumovirus* genus (HRSV – human respiratory syncytial virus), *Metapneumovirus* genus (HMPV – human metapneumovirus); of the *Picornaviridae* family, *Enterovirus* genus (HEV-D – human enterovirus D), 152 serotypes (formerly HRV – human rhinovirus); of the *Adenoviridae* family, *Mastadenovirus* genus, which includes 54 serotypes of 7 human adenoviruses (HAdV-A, HAdV-B, HAdV-C, HAdV-D, HAdV-E, HAdV-F, HAdV-G); of the *Parvoviridae* family, *Bocavirus* genus (HBV – human bocavirus) (**Table 2**). All seasonal viruses with the airborne transmission in humans belong to families with a very wide range of hosts, especially among mammals (**Table 2**).

The technology of metagenomic sequencing (or next generation sequencing), based on sequencing of the total nucleic acid and further bioinformatic analysis, has provided new opportunities for the rapid identification of already isolated viruses and for the search for new viruses directly in biological samples. The taxonomy of 80 zoonotic viruses isolated as a result of long-term monitoring in different ecosystems of Northern Eurasia has been studied using modern methods. The results of this study showed that zoonotic viruses belonging to at least 17 genera and eight families circulate in the territory of Northern Eurasia. Phylogenetic analysis of the isolated strains was performed [27]. Modern methods make it possible to analyze a virome, i. e. the entire ensemble of viruses associated with the host. Thus, metagenomic sequencing allows to quickly identify novel or divergent viruses, determine the possible source of new zoonotic infections, analyze the structure of an animal virome to control changes in its structure that lead to the emergence of new pathogens, and carry out the genomic analysis of divergent strains to improve molecular diagnostic methods. Modern molecular-genetic methods can serve as a universal tool for diagnosing viral infections directly in clinical samples [9].

Studies of the virus ecology aimed at investigating the laws of interpopulation relationships between zoonotic viruses and their vertebrate hosts in various ecosystems have been carried out in the USSR since the 1970s. An extensive program was supervised by the All-Soviet Union Center of Ecology, D. I. Ivanovsky Institute of Virology [50]. Some areas of the Center's research were comparable to the activities of the U.S. Epidemic Intelligence Service [51–53]. The main objectives were to study the ecology and evolution of zoonotic viruses that threaten biosafety, and to analyze their potential for spreading within climatic zones and various landscape zones from the Arctic to the subtropics [54, 55]. The structure of the All-Soviet Union Center of Ecology included more than 20 reference bases that worked under a single program using unified methods. An independent unit on research of birds in the framework of the All-Soviet Union Ornithological Committee was supervised by the Institute of Biology of the Russian Academy of Sciences and D. I. Ivanovsky Institute of Virology of the Russian Academy of Medical Sciences [56]. Similar research was carried out abroad in the form of an extensive program for the study of birds in Asia [57]. Another specific field of study, the features of virus circulation at high latitudes and the circumpolar spread of a number of unique zoonotic viruses, was established [58]. A special program in the field of ecology of influenza viruses in natural ecosystems and the emergence of the novel pandemic virus A/H1N1pdm2009 was implemented [25-28].

Here are some examples of the spread of viruses among different representatives of eukaryotes (**Table 5**) [60]. As a result of a long evolution, the representatives of at least the *Reoviridae* and *Rhabdoviridae* families managed to increase the number of their hosts by joining Protozoa, Plants and other eukaryotes, including humans.

The phylogenetic analysis reveals the relations of the *Iridoviridae* and *Ascoviridae* families (*Lepidoptera* insect viruses), *Mimiviridae* (viruses of protozoan), and *Poxviridae*; the *Herpesviridae* and *Myoviridae* families (archaeal and bacterial viruses). It is possible to assume the transition of *Adenoviridae* viruses from Reptiles to Birds and Even-Toed Animals. The representatives of the *Reoviridae* family have something in common with *Totyviridae* (the viruses cause latent infection of Fungi and Protozoa) and *Cystoviridae* (viruses of bacteria pathogenic for plants). In the *Reoviridae* family, the most ancient viruses

Table 5. Examples of present distribution of viruses among different representatives of Eukaryotes

Viruses		Hosts						
family	genome	Algae *(Algae)*	Plants (Plantae)	Protozoa *(Protozoa)*	Fungi *(Fungi)*	Animals (Animalia)		Human (Homo)
						Invertebrates *(Invertebrata)*	Vertebrates *(Vertebrata)*	
Endornaviridae	dsRNA, linear, 14–18 kb	+	+	–	+	–	–	–
Reoviridae	dsRNA, 9–12 segments, 19–32 kb	–	+	+	+	+	+	+
Metaviridae	ssRNA(+), 4–10 kb, presence of reverse transcriptase	–	+	–	+	+	–	–
Pseudoviridae	ssRNA(+), linear, 5–9 kb, presence of reverse transcriptase	+	+	–	+	+	–	–
Rhabdoviridae	ssRNA(–), linear, 11–15 kb	–	+	–	–	+	+	+
Iridoviridae	dsDNA, linear, 140–300 kb	–	–	–	–	+	+	–
Herpesviridae	dsDNA, linear 124–241 kb	–	–	–	–	+	+	+

were the ones of marine Protozoa (*Mimoreovirus*), Fish (*Aquareovirus*), Plants (*Orizavirus, Fijivirus*) and Transmitting Insect (*Idnareovirus, Dinovernavirus, Phytoreovirus*), Fungi (*Mycoreovirus*) [59]. Significantly later, viruses of vertebrates, i.e. birds and mammals (including humans), were formed in the presence of arthropod vectors *(Coltivirus, Orbivirus,* and *Seadornavirus*) or, in their absence, with respiratory and alimentary transmission routes (*Orthoreovirus* and *Rotavirus*), which took at least 550 million years (**Table 1**).

The above examples indicate the dependence in the formation of the population gene pool of viruses on the evolution of their hosts, which, in turn, is determined by the variability of the environment (geological cataclysms, the state of the World Ocean and atmosphere, climate, etc.). During the intertaxon viral transmission, the population gene pool provided, in particular, a change in the pathways of infection from contact (in Archaea, Bacteria, Algae, Fungi, and Protozoa) to the transmission through Arthropods (in Plants and Vertebrates), fecal-oral (Vertebrates and humans), and respiratory (humans).

The process of emergence of new viral infections in humans is determined by the high genetic variability of viruses and the ecological characteristics of their natural reservoir [60]. The main mechanism of adaptation of viruses to humans is associated with recombinations and mutations in certain regions of the viral genome. Molecular factors of pathogenicity of viruses can include genes of receptor-binding proteins, replication complex, and other regions. However, the exact mechanism of emergence and selection of such variants at the population level is still underinvestigated. It is not known which receptors are used by viruses in natural biomes and what role the intermediate host plays in overcoming the intertaxon barrier.

The description of viral diversity in natural biomes and the study of evolutionary processes leading to the emergence of novel viral infections are urgent fundamental problems and have serious applied significance in controlling the emergence of novel and reemerging viral infections and minimizing the consequences of their emergence. It is clear that epidemic emergencies that are much more serious than COVID-19 will occur in the foreseeable future. This requires joint efforts, preferably at the international level, aimed at minimizing the consequences of emerging disasters. It is necessary to constantly monitor the population gene pools of potentially dangerous viruses, first of all those capable of airborne transmission.

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