https://doi.org/10.15407/microbiolj86.06.092

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ZOONOZIC INFLUENZA VIRUSES AND THEIR RISKS FOR HUMANS

Based on a review of available literary sources and official reports, the world situation with zoonotic influenza was analyzed, and the risks related to the pandemic potential of zoonotic influenza viruses were considered. It is shown that against the background of the genetic diversity of avian and mammalian influenza viruses and their ability to reassort genes, there is a constant risk of the formation of pandemic virus variants for humans. Moreover, such an example already exists, namely the A(H1N1)pdm09 virus, which turned out to be a quaternary reassortant of swine, bird, and human influenza viruses with rapid adaptation to the human population. After the appearance of zoonotic avian influenza viruses AIV A(H5N1) in 1997, new zoonotic AIVs were discovered in the world: A(H9N2) (1998), A(H7N7) (2003), A(H7N3), A(H10N7) (2004), A(H7N9), A(H10N8) (2013), A(H5N6) (2014), A(H7N4) (2018), A(H10N3), A(H5N8) (2021), and A(H3N8) (2022). The last 3 viruses were identified during the COVID-19 pandemic. Zoonotic AIVs of different subtypes differ in their lethality in humans (for example, A(H5N1) has a 52% lethality, while A(H9N2) has a 2.2% lethality). They can also differ in their adaptation potential to the organism of mammals, particularly humans, even within the same subtype. During 2018 — 08/18/2023, 170 cases of influenza in humans caused by AIVs were registered in the world, among which A(H5N1) (10.6%) and A(H5N6) (39.4%) prevailed. Since 2021, their sharp growth has been observed (3 times compared to 2020 and 5.7 times compared to 2019). During the 2017/2018 — 2022/2023 seasons, 49 cases of swine flu caused by A(H1N1) v, A(H1N2)v, and A(H3N2)v viruses were reported in the world. Among them, A(H1N2)v prevailed (53.1%). The current trend of increasing avian influenza outbreaks among birds, mammals, and human cases with the expansion of geographic areas and the involvement of new species and categories of animals may be related to climate change, increased agricultural land, and poultry production. The increased effectiveness of epidemiological surveillance for severe respiratory syndrome, which occurred against the background of the COVID-19 pandemic, also contributed to the detection of new cases of zoonotic influenza in humans and the identification of new zoonotic influenza viruses. This requires constant monitoring of the circulation of both zoonotic influenza viruses and animal influenza viruses in general, as well as the selection of zoonotic influenza viruses — candidates for the production of vaccines in case of a worsening of the epidemic situation.

Keywords: *zoonotic influenza viruses, zoonotic influenza, surveillance, vaccines against zoonotic influenza.*

Citation: Zadorozhna V.I., Shahinian V.R. Zoonozic Influenza Viruses and their Risks for Humans. *Microbiological journal.* 2024 (6). P. 92—114. https://doi.org/10.15407/microbiolj86.06.092

The wide genetic diversity of influenza A viruses circulating among birds and mammals determines their high evolutionary and zoonotic potential. This is facilitated by the structure of the influenza A virus genome, which is represented by a single-stranded RNA that has 8 segments, about 14,000 nucleotides and encodes at least 10 proteins. Given the presence of such evolutionary mechanisms as antigenic drift (gradual accumulation of point mutations) and gene reassortment (from different influenza A viruses during co-infection), there are constant risks of the formation of new human influenza viruses capable of overcoming interspecies barriers and acquiring pandemic potential.

Generally, there are 4 genera of influenza viruses, which are classified on the basis of nucleoprotein (NP): A, B, C and D. They belong to the *Orthomyxoviridae* family. For humans, viruses of genera A and B, rarely C, are of epidemiological and clinical significance. Among zoonotic viruses, influenza A viruses are considered from this point of view. In contrast to influenza B, C and D viruses, influenza A viruses are characterized by the antigenicity of surface glycoproteins (hemagglutinin (HA) and neurominidase (NA)) are divided into 16 HA- and 9 NA-subtypes. With the exception of bat influenza-like viruses H17N10 and H18N11, all subtypes of influenza A viruses were originally isolated from birds as species hosts (Mostafa et al., 2018).

The last example of a new influenza virus that caused a pandemic in 2009-2010 was the A(H1N1)pdm09 virus. It turned out to be a quadruple reassortant, 5 segments of the genome of which originate from the swine influenza virus, 2 from avian, and 1 from human (Garten et al., 2009; Zadorozhna et al., 2016). A new parasitic system was formed very quickly, in the process of circulation, the virulence of the virus decreased, and the layer of the unfavorable population gradually increased due to natural infection or vaccination. For now, this virus has been transferred to the seasonal category and included in seasonal vaccines. Its antigenic drift is traced, which requires periodic replacement of vaccine strains of the virus with antigenically relevant variants.

As for the highly pathogenic avian influenza A (HPAI) viruses (classified by their pathogenicity to chickens), which are attracting the most attention as potential etiologic agents of future pandemics, their highly pathogenic phenotype was thought to be limited to subtypes H5Nx, H7Nx, and H9N2, which carry a multibase cleavage site in its HA protein (Steinhauer, 1999; Mostafa et al., 2018). In addition, the possibility of a low-pathogenic virus' acquiring the HPAI potential, as happened with the A(H5N6) virus in 2014 (Zadorozhna et al., 2016), is not excluded. But as further studies show, it is impossible to exclude viruses of other subtypes from those that can pose a danger to humans.

Every year there are reports of individual cases or group diseases of humans with zoonotic influenza associated with certain subtypes of the influenza A virus. This situation requires constant virological and epidemiological monitoring in order to be prepared to prevent and counter a potential pandemic.

In addition to the risk of increasing the number of human cases, bird flu also has economic consequences due to the culling of millions of birds. This leads to significant economic losses. For example, more than 5.5 million birds were culled from October 2021 to November 2022 in Great Britain due to the bird flu virus. The outbreak of bird flu in the USA in 2022 led to the death of about 40 million animals and various economic losses in the range of $2.5 to $3 billion (Farahat et al., 2023). The above emphasizes the importance of this problem, which should be considered and solved within the framework of the concept of «One Health».

The **purpose** of the work was to analyze the properties of the most relevant zoonotic influenza A viruses that caused disease in humans dur-

ing the past 5 years (2019 — August 2023) and to assess the risks associated with them.

All human cases of influenza caused by new influenza virus variants are fortifiable to WHO in accordance with the International Health Regulations (IHR) (2005). All infections in poultry caused by avian influenza virus (AIV) of any subtype fulfilling the in vivo criteria for high virulence laid down in the Terrestrial Animal Health Code of the World Organization for Animal Health (OIE) (ECDC, 2022).

Table 1 presents cases of zoonotic influenza in humans, in particular those caused by viruses new to humans, for the period 2018 — August 2023, information on which is provided by the WHO on its website «Disease Outbreak News» (WHO, 2023).

Cases involving novel human AIVs, namely A(H7N4) (2018), A(H10N3) (2021), and A(H3N8) (2022), were reported during this period. It should be noted that during 2019, there were no reports of cases of zoonotic influenza among humans on the WHO website. There is also no report of AIV A(H5N8), which was first identified in humans in 2021 (WHO, February 26, 2021). At the same time, information about all cases of bird flu in humans is also provided by the WHO in its weekly bulletins, which we will talk about below. Although Table 1 does not list all cases of zoonotic influenza that occurred in humans during this period in the world, there is a clear trend toward an increase in the sensitivity of its surveillance, especially since the second year of the COVID-19 pandemic. This is also emphasized by the WHO (WHO, November 19, 2021). Indirect confirmation of this thesis is the identification during 2021—2022 of four new to humans AIVs.

This was carried out both due to the virological testing of most cases of severe acute respiratory syndrome, as well as within the framework of routine influenza surveillance. In 2020, 2021, and 2022, the ability of 3 more subtypes of avian viruses to cause disease in humans was determined for the first time: A(H5N8), A(H10N3), and A(H3N8), respectively. At the same time, it should be noted that this situation was observed against the background of a sharp decrease in the circulation of seasonal influenza viruses, especially during the first 2 years of the pandemic. The molecular genetic study of the selected strains made it possible to determine their genetic diversity and obtain additional information on the directions of their evolution and the risks of adaptation to the human population.

Avian influenza A viruses. AIVs include the largest number of emergent and re-emergent viruses, causing particular concern due to the potential risk of a pandemic with catastrophic

Table 1. **Information on cases of zoonotic influenza A in humans, registered during 2018 — August 2023** [7]

No.	Message date	Subtype of influenza A virus	Country	Cases (n)	Age of patient (years)	Severity of disease outcome	Note
2018							
1	22.02	**H7N4***	China	1	68	recovery	1st case in the world. Occurred against the background of coronary disease and hypertension
2	23.03	H1N2	Netherlands	1	2	easy / recovery	The virus is a reassortant of seasonal viruses A(H1N1)pdm09 (HA and nonstructural protein (NS) genes) and A(H3N2) (other genes)

Continuation of Table 1

No.	Message date	Subtype of influenza A virus	Country	Cases (n)	Age of patient (years)	Severity of disease outcome	Note
2019							
There was no WHO notification about outbreaks of zoonotic influenza among people							
2020							
1	09.07	H1N2	Brazil	1	22	recovery	Virus A(H1N2)v. 2nd episode in the region (1st in 2015)
2021							
2	04.01	H1N2	Brazil	1	4	recovery	Virus A(H1N2)v. 3rd case in the country, total 27 (from 2005)
3	05.02	H3N2	US	1	<18	recovery	Virus A (H3N2)v. Related to viruses circulating in swine in the US in 2019—2020, 437 cases (from 2005), all in the US
4	10.06	**H10N3***	China	1	41	recovery	1st case in the world
5	16.08	H5N1	India	1	<18	serious / fatal	The patient had a mixed infection (influenza B)
2022							
6	14.01	A(H5)	United Kingdom	1	unknown	asymptomatic	The case arose against the background of H5N1 poultry flu
7	06.05	H5N1	US	1	adult	easy / recovery	1st case in the USA
8	09.05	**H3N8***	China	1	4	easy / recovery	1st case in the world
9	19.05	H1N1	Germany	1	30-40	easy / recovery	Eurasian avian swine virus A(H1N1)
10	03.11	H5N1	Spain	1	19	asymptomatic	The case arose against the background of H5N1 influenza at a poultry farm
2023							
11	06.04	A(H5)	Chile	1	53	serious/ recovery	
12	11.04	**H3N8***	China	1	56	serious / fatal	3rd case in China and the world (2nd — in May, easy)
13	21.04	A(H5)	Chile	1	unknown	serious/ recovery	The virus is 99.9% identical in HA, and 100% identical in NA to the bird virus in Chile
14	16.07	H1N1	Brazil	1	42	serious / fatal	Virus A(H1N1)v. 99% identity by NA with A(H1N1)v circulated in 2022
15	11.08	H1N2	US	1	18	moderate severity/ recovery	Virus A(H1N2)v. 37th case of A(H1N2)v in the US. From 2005, 512 cases of influenza A virus infection (all subtypes) were registered in the world

* These viruses were isolated from humans for the first time

Table 2. **Dynamics and number of registered cases of avian flu in the world, caused by viruses of different subtypes,**

Virus subtype		2018	2019
A(H5N1)	N cases, starting from the 1st case/ fatal	860/454	861/455
	N cases per year	0	1
A(H5N6)	N cases, starting from the 1st case/ fatal	23/ unknown	24/ unknown
	N cases per year	6	1
A(H7N4)	N cases, starting from the 1st case/ fatal	1	1
	N cases per year	1	0
A(H7N9)	N cases, starting from the 1st case/ fatal	1567/616	1568/616
	N cases per year	2	1
A(H9N2)	N cases, starting from the 1st case/ fatal	22	28
	N cases per year	7	6
A(H3N8)	N cases, starting from the 1st case/ fatal	—	—
	N cases per year		
A(H10N3)	N cases, starting from the 1st case/ fatal	—	—
	N cases per year		
Total number of cases per year		16	9

consequences. The increase in the number of domestic animals and poultry worldwide is accompanied by an increase in the number of registered outbreaks of avian influenza among people (Philippon et al., 2021). The transmission of AIVs among their species hosts is largely related to the characteristics of their HA. AIVs preferentially recognize cell receptors containing sialic acid (SA), which is linked to galactose via an α2,3-linkage (SAα2,3Gal), whereas human influenza viruses preferentially recognize SAα2,6Gal. The acquisition of the SAα2,6Gal specificity by the zoonotic influenza virus is one of the changes that can lead to pandemics (Auewarakul et al., 2007).

The dynamics and number of registered cases of avian influenza caused by viruses of various subtypes among people over the past 5 years, calculated by us based on the data of weekly WHO bulletins, are given in Table 2. Starting from 2021, there is a sharp increase in registered cases of avian influenza (by 3 times compared to 2020 and by 5.7 times compared to 2019). Among the total number of registered cases (170 cases), those caused by viruses A(H5N1) (10.6%) and A(H5N6) (39.4%) prevailed.

Avian influenza viruses of subtypes A(H5). In total, 9 subtypes of A(H5) viruses are known, namely A(H5N1), A(H5N2), A(H5N3), A(H5N4), A(H5N5), A(H5N6), A(H5N7), A(H5N8), and A(H5N9). Most of the A(H5) viruses circulating among wild birds and poultry are of low pathogenicity, but HPAI is sometimes detected. The first is the A(H5N1) virus, which has caused severe pneumonia and death in about 50% of cases. Also, since 2014, the A(H5N6) virus has been a major concern, and the human morbidity caused by it is accompanied by a mortality rate of 40%. It also became known about the infection of people with HPV A(H5N8) in 2020 (CDC, *Influenza Type A Viruses*). Numerous reassortant strains of new HPAV A(H5) clade 2.3.4.4 continue to emerge and spread, particularly in Asia, Europe, and North America, such as subtypes H5N2, H5N5, H5N6, and H5N8) (Yang et al., 2015).

HPAI virus A(H5N1). The first cases of influenza in humans, etiologically related to HPV

among people over 2018 — 08/18/2023

	2020	2021	2022	2023 (up to 08/18/2023)	Cases (n) 2018 — 08/18/2023
	862/455	863/456	868/457	878/458	
	1	1	5	10	18
	27/ unknown	58/27	83/ unknown	86/33	
	3	29	25	3	67
	1	1	1	1	
	0	0	0	0	1
	1568/616	1568/616	1568/616	1568/616	
	0	0	0	0	3
	41	61/2	82/2	90/2	
	13	20	21	10	77
	—	—	2	3	
			2	1	3
	—	1	1	1	
		1	0	0	1
	17	51	53	24	170

IA(H5N1), were reported in Hong Kong during the outbreak among poultry in 1997.

The greatest number of diseases caused by this virus in humans was observed during 2004—2016. At that time, the A(H5N1) virus was considered one of the main contenders for a future pandemic. In the future, despite the panzootic nature of A(H5N1) for wild and domestic birds, after a long period of isolated cases or no cases at all during the year, since 2022 there has been again a slight increase in morbidity caused by this virus.

Starting from 1997 to August 18, 2023, 896 cases of avian influenza caused by different clades of HPAI A(H5N1) among people were registered in 23 countries of the world (Fig. 1) (CDC, 2023; WHO, August 18, 2023).

The cumulative share of fatal cases was 52% (458 cases). The highest annual incidence among humans was registered in 2015 (145 cases in 4 countries). This was due to the large outbreak in Egypt (136 cases). The incidence was also high in 2006 (115 cases in 9 countries).

During 2018—2021, there were single cases in the same years. Starting from 2022, there is a trend toward an increase in morbidity. From January 2022 to June 29, 2023, 13 sporadic human cases were reported in 8 countries (UK — 2, Vietnam — 1, Ecuador — 1, Spain — 2, Cambodia — 2, China — 1, USA — 1, Chile — 3), including 6 with severe clinical course, of which 2 cases of death, 2 cases of mild course, and 5 asymptomatic cases. According to the results of sequencing, the viruses were assigned to clade 2.3.2.1c (2 viruses, Cambodia) and clade 2.3.4.4b (10 viruses, the other countries, except for Vietnam, where the clade is unknown). Any genetic markers that demonstrate a decrease in sensitivity to topical antiviral drugs have not been found (CDC, 2023).

The diagnosis of avian influenza A(H5N1) is based on clinical, laboratory, and epidemiological criteria. Laboratory criteria are at least one of the following: isolation of HPAI A(H5N1) from a clinical specimen; detection of influenza A(H5) nucleic acid in a clinical specimen; influenza A(H5) specific antibody response (4-fold or greater rise or single high titer).

Despite the fact that a greater proportion of patients who became ill with avian influenza

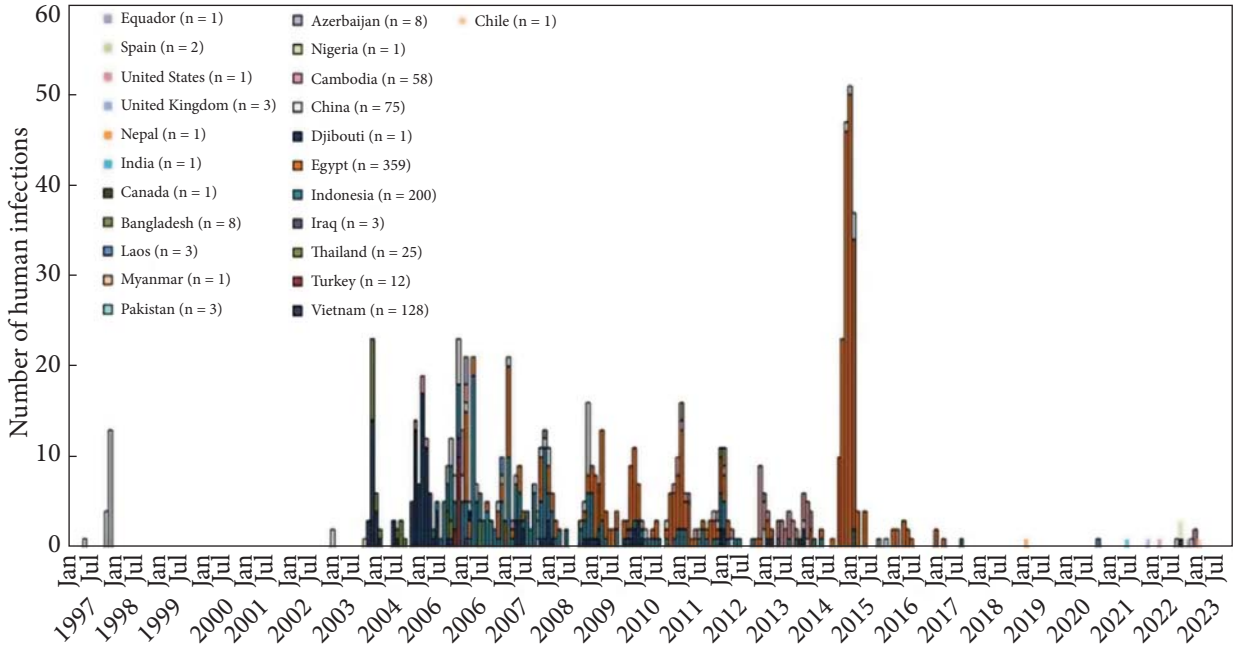

Fig. 1. Epidemic curve of humane cases of A(H5N1) in the world by the illness onset date over 1997 — 2023 (N=896)

caused by the A(H5N1) virus were infected through direct contact with birds, as early as 2008 WHO reported of transmission of the virus from person to person with a predominance of 2—3 confirmed epidemic connections. Herewith, the largest number of patients was 8 (Update on Avian Influenza A(H5N1) Virus Infection, 2008).

Substitutions in positions 129 and 134 of the HA gene (L129V and A134V mutations) identified in a virus isolated from a deceased patient were described. The authors showed that these mutations can change the binding preference of NA receptors of the A(H5N1) virus with SAα2,3Gal to both SAα2,3Gal and SAα2,6Gal receptors. The possibility of selecting and reproducing this mutant with specificity for SAα2,3Gal and SAα2,6Gal receptors in the human population has been shown (Auewarakul et al., 2007).

Research was also conducted on the experimental adaptation of this virus for respiratory transmission among animals. Molecular changes in the HA that would allow a virus having an H5 subtype HA to be transmitted among mammals were evaluated. The authors identified a reassortant virus containing HA from the A(H5N1) virus with 4 mutations and 7 other gene segments of the pandemic A(H1N1)(pdm09) virus with an airborne transmission mechanism. The transmissible reassortant H5 virus preferentially recognized human-type receptors, replicated efficiently in ferrets, caused lung damage and weight loss but was not highly pathogenic or lethal. These results show that the HA of H5 can be converted into an HA that supports efficient transmission of the virus in mammals. However, the authors could not state whether the 4 mutations they identified in HA (H5) are able to fully ensure the transmissibility of the A(H5N1) avian virus (Ima et al., 2012).

Molecular genetic studies of A(H5N1) viruses seen in humans are now continuing. Thus, the HA protein (H5) of the virus (strain *A/India/NIV-SARI-4571/2021*), seen in an 11-year-old child in India in 2021, who died of avian flu against the background of acute myeloid leuke-

mia, has the motive site splitting basic amino acids (PQRERRRKR*G), which indicates that it belongs to VPVG clade 2.3.2.1. The sequence of the receptor binding site with 220 loops between amino acids Q222 and G224 has lost its conservation value for the α 2—3 pt receptor. There have been no mutations in the NA and matrix 2 genes, which are responsible for NA inhibitors and resistance to amantadine. The virus has lost its ability to adapt to birds and does not have the necessary markers of adaptation to mammals or pathogenicity to humans (Potdar et al., 2022).

An unprecedented outbreak of influenza A(H5N1) among domestic and farm poultry, wild birds, and marine mammals in early 2023 is reported in Chile. At the same time, the A(H5) virus was isolated from a patient as part of routine surveillance for severe acute respiratory infections (WHO, April 6, 2023).

The outbreak of this infection among cats in Poland in 2023 was unexpected. The notification about the detection of abnormal cases of death among cats in the country from the National Coordinator of the International Health Regulations to the WHO was received on 06/27/2023. As of 07/11/2023, 47 samples were examined, taken in 46 cats and 1 captive caracal, 29 of which were positive for the influenza A(H5N1) virus. 11 cats died, and 14 were euthanized. The last case of death was registered on June 30. The source of infection of the cats is currently unknown, an epizootological investigation is underway. WHO notes that sporadic cases of infection of cats with the A(H5N1) virus had been noted before, but this is the first case of their mass infection in a wide geographical area within one country. As of July 12, 2023**,** there were no cases of symptoms of the disease among people who came in contact with the infected cats, and the period of medical observation of all contact persons passed (WHO, July 16, 2023). The fact that people are in closer and more frequent contact with cats than with birds and the trend of increasing incidence of this infection among people require further monitoring, in particular with regard to the risk of adaptation of the virus to the human organism.

AIV A(H5N6). The first disease in humans caused by this virus was registered in 2014. Before that, the pathogen had been known for many years as a low-pathogenic bird virus. The virus that caused the disease in humans turned out to be a new highly pathogenic triple reassortant. The HA gene of the virus was similar to subtype H5 of clade 2.3.4.4; according to the NA gene — to the group of A(H6N6) viruses that circulated among domestic ducks in Northern China. The internal genes were highly related to similar genes of strain A(H5N1) *A/wildduck/Fujian/1//2011* clade 2.3.2.1.b; according to amino acid sequences, NA had a more pronounced affinity for α2-3-sialic receptors. At the beginning of 2016, 9 cases had been registered. In particular, 4 were fatal (Zadorozhna et al., 2016).

In 2022, the total number of registered cases caused by this virus was already 76 (Zhang et al., 2022). However, it is noteworthy that 54 of them occurred in 2020—2022 (2020 — 5 in China, 1 in Russia, 2021 — 1 in Laos, 36 in China (including 18 fatal), 2022 — 11 in China) (Farahat et al., 2023). On August 18, 2023, the number of cases was already 86, including 33 fatal cases (38%) (WHO, August 18, 2023).

This raises concerns about the further behavior of this virus, in particular the risk of its adaptation to the human population.

It is assumed that in all known cases of human influenza caused by the A(H5N6) virus, infection occurred through direct contact between a person and a bird. Some sources emphasize that early detection of infected people and prevention of an increase in the number of cases is likely to reduce the ability of the virus to mutate, reducing the possibility of its transmission among people (Patel et al., 2021).

At the same time, significant genetic changes have been reported in those variants of the virus that currently circulate among birds and cause disease in humans. Thus, according to the results of the phylogenetic analysis of 10 A(H5N6) strains isolated from domestic birds (ducks, geese, chickens) in one of the provinces of China, in particular, in those households where cases of influenza in humans were registered, reassortment of different genes with avian viruses was observed in influenza of other types (with A(H3N2) — by the main polymerase gene and non-structural genes of PB2, with A(H1N2) — by the PB1 gene, with A(H5N8) — by the NA gene and matrix genes, and with A(H5N6) — by the gene NA). At the same time, all viruses had S137A and T192I mutations in the HA gene, which allow it to bind to the human SAα2,6Gal receptor, thereby increasing human susceptibility to the virus. Adaptive mutations to the mammalian organism (T33K, L89V and G309D) were detected in the PB2 gene of all strains, which increases the virulence of A(H5) viruses in mice. These mutation variants were rarely found in previously circulating A(H5N6) viruses. The authors suggest that the new A(H5N6) virus is a recombination of A(H5N8) and A(H5N6) viruses. It was found that other low-pathogenic AIVs also participated in recombination, as a result of which the internal genes of all strains seem complex and, at the same time, contradictory (Chen et al., 2022).

The variety of gene recombination of A(H5N6) viruses was revealed in the study of viruses isolated from patients who fell ill in China in 2021. Thus, in the study of 5 strains, all of them had NA and matrix protein genes from the A(H5N8) virus, NA — from A(H5N6), PB1 — from A(H1N2), PB2 — from A(H5N8) (4 strains) and A(H1N2) (1 strain); NP — from A(H5N6) (3 strains), A(H3N2) (1 strain), A(H4N6) (1 strain); NS — from A(H3N2) (3 strains), and A(H5N6) (1 strain) (Xiao et al., 2021). In a study of an *A/chicken/Chonqqing/H1/2021(H5N6)* (CK/CQ/H1) virus isolate isolated from a bird wash in a market in China visited by a person with confirmed avian influenza A(H5N6), most of the genes of avian and human A(H5N6) isolates were closely related. Analysis of the HA amino acid sequence showed the presence of a cleavage site, which indicates the high pathogenicity of the virus for chickens. The presence of receptor binding sites Q226 and G228 indicates that the isolate will preferentially bind to avian receptors, however receptor binding site mutations of A137, N158, A160, N186, I192, Q222, and R227 may increase binding to human receptors. The virus also showed excellent antigenicity against the Re-11 vaccine strain, which has been used in China to vaccinate poultry since 2019. The obtained results indicate that new A(H5N6) infection in poultry and humans is needed to prevent and control antigen-compatible vaccines and more effective preventive measures (Jiang et al., 2022).

New for humans HPAI A(H5N8) virus. In February 2021, WHO reported on the identification of a novel human influenza A(H5N8) virus in 7 people in russia during an outbreak among poultry on a poultry farm. Cases were asymptomatic. Also, during December 3—11, 2020, 101,000 out of 900,000 chickens died on the farm. The viruses belonged to clade 2.3.4.4b. In 2020, A(H5N8) viruses were also detected in poultry or wild birds in Bulgaria, the Czech Republic, Egypt, Germany, Hungary, Iraq, Japan, Kazakhstan, the Netherlands, Poland, Romania, Great Britain, and Russia (ECDC, 2022).

In late 2021, HPAI A(H5N8) clade 2.3.4.4b was detected in domestic ducks in a poultry mart in Cambodia (Edwards et al., 2023). HPAI A(H5N8) became a problem for poultry farming in some countries of the world even earlier. Thus, starting in 2018, in Egypt, its share among samples positive for the influenza virus increased from 23% in 2017 to 66.6% in 2018. Among the reasons for the relative growth of

the role of A(H5N8) compared to A(H5N8), researchers do not rule out the lack of appropriate vaccines against clade 2.3.4.4b viruses (Hassan et al., 2021). In a study of A(H5N8) viruses isolated in Egypt during 2019—2022 from broiler chickens that died due to respiratory infection, the frequency of detection of A(H5N8) was 21.6% of the number of birds examined. At the same time, this indicator was 22.3% among vaccinated birds, and 12.5% among unvaccinated birds. Virus samples obtained during 2020—2022 had 10 nucleotide mutations in the HA gene (R72S, A83D, and T140A). It is emphasized that ARVH A(H5N8) poses a threat even to vaccinated birds, which requires periodic molecular monitoring with evaluation of the effectiveness of vaccines and the use of preventive strategies (Setta et al., 2023).

In October 2020, 13 A(H5N8) clade 2.3.4.4b viruses were identified in wild ducks in China. They were genetically related to viruses circulating mainly among poultry in Europe at the beginning of 2020. The movement of wild ducks infected with the A(H5N8) virus was also traced (Lv et al., 2022).

In Egypt, an evaluation of the effectiveness of commercial vaccines for vaccination of broiler chickens was carried out, since poultry vaccination is widely used in the country. An A(H5) vector vaccine derived from recombinant turkey herpesvirus rHVT-H5 clade 2.2 was evaluated alone or in combination with a commercial inactivated genetically engineered H5N1 (rgH5N1) vaccine (clade 2.2) for the prevention of influenza, etiologically related to genetically modified virus A(H5N8) clade 2.3.4.4b. It was shown that the simultaneous use of rHVT-H5 and rgH5N1 vaccines in the vaccination calendar on poultry farms is the most effective preventive tool (mortality and virus shedding) against this variant of influenza (El-Shall et al., 2021). For comparison, it should be noted that studies conducted in Turkey earlier, before the appearance of the new genetic variant A(H5N8), demonstrated complete protection of the vaccine rHVT-H5 against the virus of this subtype circulating at that time (Steensels et al., 2016). In general, it is not excluded that the widespread use vaccines for the immunization of birds to a certain extent can contribute to the acceleration of mutations of influenza viruses and the acceleration of their evolutionary changes.

New to humans AIV A(H3N8). AIV A(H3N8) viruses are among the most common subtypes in wild birds and are found in live bird markets in Asia with no signs of disease. There are currently 3 known cases of influenza in China caused by this virus in humans. The first case was registered in a 4-year-old child in April 2022 and had a mild course. Contact with poultry on the homestead and participation in the preparation and consumption of chicken before the onset of symptoms have been reported. A(H3N8) RNA was detected in a nasopharyngeal swab from a dog, an anal swab from a cat, and environmental samples collected at the patient's home. The full-length sequences of the HA viruses from the dog and cat were identical to the HA virus sequences from the patient. No flu-like illnesses were observed in the patient's family members, and viral RNA was not detected in them either. At the same time, neutralizing antibodies against the ZMD-22-2 virus were detected in the patient and 3 members of his family. The second case with a severe course was observed in a 5-year-old child after visiting a live poultry market in May of the same year. The distance between these cases was 620 km. The third was a 56-year-old woman who fell ill in February 2023. She developed pneumonia, which ended fatally (ECDC, 2023; WHO, 2023; Bao et al., 2022).

Upon further investigation, it was determined that the A(H3N8) virus, which began to cause disease in humans, was first detected on a poultry farm in Guangdong Province in December 2021, and subsequently in several other provinces. Genome sequencing of the isolated viruses showed that the new A(H3N8) was formed

by multiple gene recombination. The HA gene could have originated from the H3Ny duck virus. The NA gene belongs to the North American lineage and may have originated in Alaska (USA) and was transferred as a result of the migration of birds along the East Asian lineage. 6 internal genes of the new variant of the virus came from the influenza virus A(H9N2) genotype G57 endemic to chicken flocks. Gene recombination events may have occurred among domestic ducks or chickens in the Pearl River Delta region of Southern China. New A(H3N8) viruses have the ability to bind to sialic acid receptors of both avian and human type, which carries risks for humans (Yang et al., 2022).

Thus, all the genes of the new variant of the virus are of avian origin. 2 human isolates (*A/Henan/4-10CNIC/2022* — the 1st case and *A/Changsha/1000/2022* — the 2nd case) are new triple reassortants of avian A(H3N8) viruses (ECDC, 2023).

Recent studies show th0at A(H3N8) viruses are able to infect and efficiently replicate in organotypic normal human bronchial epithelial cells (NHBE) and lung epithelial cells (Calu-3). Human isolates of the A(H3N8) virus were more virulent and caused severe pathology in mice and ferrets compared to chicken isolates. Importantly, the A(H3N8) virus isolated from a patient with severe pneumonia, was transmitted among ferrets by airborne droplets; it gained the advantage of binding to the human receptor and the PB2-E627K amino acid substitution required for airborne transmission. The authors predict that the human population, even with human A(H3N2) vaccination, may be susceptible to the new mammalian-adapted HPIA A(H3N8) on the epidemic or pandemic scale (Sun et al., 2023). This requires continual molecular genetic monitoring of the evolution of this virus.

AIVs of subtypes A(H7). AIVs of subtypes A(H7), such as A(H7N2), A(H7N3), A(H7N4), A(H7N7), and A(H7N9), have been proven to be capable of infecting humans, as well as A(H7) viruses with low pathogenicity of the H7 subtype are able to acquire the properties of high pathogenicity due to mutations. This poses a potential threat to public health (Wang et al., 2023).

AIV A(H7N4). So far, only 1 laboratory-confirmed case of influenza caused by this virus is known. It occurred in December 2017 in a 68-year-old woman in China, but was only reported by WHO in February 2018 (WHO, 2023, 18 August; Tong et al., 2018). Later, active surveillance in high-risk areas in Cambodia identified several low-pathogenic influenza A(H7) viruses, mainly in ducks. None belonged to the A/Anhui/1/2013(H7N9) lineage; however, some A(H7) viruses since 2018 have shown temporal and phylogenetic similarity to the H7N4 virus that caused disease in China in 2017 (Vijaykrishna et al., 2019).

AIV A(H7N9). Cases of human infection with a new reassortant virus of avian influenza A (H7N9) began to be registered at the beginning of 2013. It was confirmed that this virus was low pathogenic for poultry at that time (Liu et al., 2014). It was isolated from respiratory samples obtained from three patients and identified as A(H7N9) (strains *A/Anhui/1/2013*, *A/Shanghai/2/2013*, *A/Shanghai/1/2013*). Sequencing analysis showed that all genes of these 3 strains were of avian origin and had 6 internal genes from AIV A (H9N2). The Q226L (H3-numbering) substitution in the 210-loop of the HA gene was detected in 2 strains (*A/Anhui/1/2013* and *A/Shanghai/2/2013*). All 3 viruses had a T160A mutation in the 150-loop NA gene and a deletion of 5 amino acids in NA. All 3 patients had fever, cough, and shortness of breath, and the disease ended fatally. 2 patients had a history of recent contact with poultry. Among the complications, acute respiratory distress syndrome and multiple organ failure were observed (Gao et al., 2013).

During 2013—2017, A(H7N9) virus caused 5 severe epidemic waves of influenza among

humans in China (Guinat et al., 2023). In early 2017, the A(H7N9) virus became highly pathogenic for birds, posing a major threat to human health and devastating losses to poultry farming. Subsequently, nationwide vaccination of chickens in China with a bivalent inactivated H5/H7 avian influenza vaccine, which began in September 2017, allowed for control of avian influenza A(H7N9) in poultry and prevent human infection (Li et al., 2021).

In 2018, WHO reported that all but three cases of influenza A(H7N9) were reported in China. During the most recent 6th wave, which began in October 2017, only 3 human cases were identified. In addition, the circulation of this virus among poultry and in the environment decreased (WHO, September 5, 2018). The last human case of influenza A(H7N9) was registered in 2019. At that time, 1568 confirmed cases of this infection were known, including 616 fatal cases (39%) (WHO, August 18, 2023).

To determine the adaptation potential of the new A(H7N9) virus to the human body, the genetic changes in the virus during passages on primary epithelial cells of the human respiratory tract (hAEC) were studied. After 35 serial passages, 6 amino acid mutations were detected, particularly in HA (R54G, T160A, Q226L, and H3-numbering), NA (K289R or K292R, N2-numbering), NP (V363V/I), and PB2 (L/R332R). Mutations in HA increased the affinity of binding to SAα2,6-Gal receptors (from 39.2% to 53.4%), however, increased viral replication was not observed due to an increase in the level of cell cytokines (IL-6, MIP-1α, and MCP-1). The obtained results allowed the authors to talk about the existence of a possible evolutionary obstacle for the effective transmission of AIV A(H7N9) from person to person (Huang et al., 2017).

Retrospective studies have shown that the A(H7N9) virus circulated among humans and birds in poultry marts for weeks to months before it was first detected. The seasonality of transmission of the A(H7N9) virus was confirmed, and it is assumed that a large number of cases of infection were not taken into account (Guinat et al., 2023).

Given the sufficiently high mortality rate among those infected with influenza A(H7N9), the WHO has created interim biosafety guidelines for laboratories working with human samples when the presence of this virus is suspected or confirmed (WHO, January 12, 2018). It has been recommended that such material, if not associated with virus reproduction, be handled at biosafety level 2 (BSL-2), while isolation or propagation of the A(H7N9) virus be carried out at a higher biosafety level (BSL-3 or above).

AIV A(H9N2). For now, 90 cases of influenza A(H9N2) in humans have been registered in the world (88 in China, 2 in Cambodia), including 2 fatal cases in patients with concomitant pathology (2.2%). The last case was observed in June 2023 and ended with recovery (WHO, August 18, 2023).

Although the influenza A(H9N2) virus is considered low pathogenic, its pandemic potential was discussed in the scientific literature as early as 2009 (Alexander et al., 2009). The peculiarities of its circulation and properties were described in detail by us earlier (Zadorozhna et al., 2016). It was noted then that it cannot only be the cause of bird flu in humans but can also be a gene donor for other bird flu viruses, including zoonotic ones such as A(H7N9) and A(H10N8) (Sun & Liu, 2015). The expressed potential of the A(H9N2) virus circulating between birds and humans with regard to interspecies transmission, the contribution to the formation of new reassortants, and the emergence of new pandemic subtypes continue to be subjects of study (RahimiRad et al., 2016). As for the formation of new reassortants, it has been found that this also applies to the new human viruses A(H3N8) and A(H10N3), in which the internal genes also come from the influenza virus A(H9N2) (Yang et al., 2022; Zhang et al., 2023).

Unlike HPVI subtypes A(H5) and A(H7), A(H9N2) viruses have not been a priority for control in many countries. However, A(H9N2) has gradually become the dominant subtype in poultry in China since 2016, which has also contributed to the emergence of new subtypes of human pathogenic influenza viruses (eg, A(H10N3) and A(H3N8)). During planned surveillance in China during 2019—2020, 22 viruses A(H9N2) were isolated from chickens. Phylogenetic analysis showed the existence of 3 independent clades of the virus based on HA genes, which indicates the recent evolution of its genomes and the formation of 3 new antigenic variants. The bivalent HN/SD chicken vaccine that had been used against this virus for 20 years was also shown to be ineffective against new A(H9N2) variants. The constant appearance of influenza viruses with internal A(H9N2) genes infecting people demonstrates the pandemic potential of A(H9N2) viruses and indicates the need to urgently stop the generation of new AIVs. The authors emphasize the need to develop universal vaccines against A(H9N2) (Zhang et al., 2023).

Other authors also report on the rapid evolution of the A(H9N2) virus. This happens due to the movement in live poultry marts from different regions and people's contact with them. It is important to reduce interregional trade in live poultry and to strengthen the monitoring of AIVs in marts to reduce the spread of AIVs (Liu et al., 2023).

AIVs of subtypes A(H10). Known subtypes of A(H10) viruses include A(H10N3), A(H10N4), A(H10N5), A(H10N6), A(H10N7), and A(H10N8). A(H10N4) was identified in mink in 1984, and A(H10N5) in pigs in 2008. Viruses of the A(H10) subtypes currently causing human disease include A(H10N3), A(H10N7), and A(H10N8). The first human case of influenza A(H10N7) was reported in Egypt in 2004, followed by Australia in 2010. The first human case of influenza A(H10N8) was observed in China in 2013. Most human cases caused by A (H10) is a result of contact with infected poultry (CDC: *Influenza Type A Viruses*).

New to humans AIV A(H10N3). On 05/31/2021, China reported to WHO the first confirmed case of human infection with AIV A(H10N3) in the world. A 41-year-old man developed fever and nausea on 04/23/2021and was hospitalized on 04/28/2021 to the intensive care unit of the local hospital. The patient recovered. The patient had no clear history of contact with birds. No A(H10N3) virus was detected in the local surroundings and among poultry. Contact persons did not have any symptoms. This case was considered an accidental bird-to-human infection with a low probability of subsequent human-to-human transmission (WHO, 2021, 10 June).

Although no further human cases of this virus have been reported, studies of A(H10N3) viruses isolated from chickens from a live poultry mart have yielded alarming results. Genome sequencing of 3 strains (*A/chicken/Jiangsu/0146/2021* (JS146, H10N3), *A/chicken/Jiangsu/0169/2021* (JS169, H10N3), and *A/chicken/Jiangsu/0189/2021* (JS189, H10N3)) showed their high homology to the human H10N3 isolate. They proved to be highly pathogenic in mice, effectively replicating in the nasal conchae and lungs of mice while maintaining binding affinity to the avian receptor. Viruses also effectively multiplied in A549 cells and chicken embryos. Strain JS146 was sensitive to neuraminidase drugs, oseltamivir, and zanamivir. Strains JS169 and JS189 were more resistant. Genetic comparison showed that drug resistance was due to a substitution at position 368 NA. It is also important that several key molecular markers associated with adaptation to mammals have been identified in both avian and human influenza A(H10N3) viruses, namely HA (G228S), PB2 (I292V, A588V), PB1 (M317V, I368V), and PA (A343S, K356R, S409N). These data contribute to a new understanding of the biology of this po-

tentially zoonotic virus and confirm the need for continuous epidemiological monitoring of the A(H10N3) virus (Guo et al., 2022).

During 2014—2021, 20 A(H10N3) viruses isolated from live poultry marts were studied. It was shown that viruses of the last reassortant genotype yet in 2019 received HA genes from A(H10) duck viruses and NA — from A(H7N3), internal genes from chicken viruses A(H9N2). 2 strains among the studied viruses had a higher affinity for human-type receptors than for avian ones, which indicates a potential risk of their transmission from birds to humans. Only viruses belonging to the last reassortant genotype were pathogenic for mice; 2 strains had the ability to be transmitted among ants through direct contact and 1 — by airborne transmission, but with limited efficiency. These findings emphasize the need for enhanced surveillance of A(H10N3) viruses (Zhang et al., 2023).

Influenza virus A(H10N7). The virus was first isolated in 2004 in Egypt from two one-year-old children with fever and cough, whose father was a poultry trader. These cases of the disease ended in recovery. Also, in 5 cases, the same virus was isolated from wild ducks from the hunting market of migratory birds (PAHO, 2004). In March 2010, an outbreak of low-pathogenic avian influenza A(H10N7) occurred on a chicken farm in Australia. Seven farm workers slaughtering healthy poultry reported conjunctivitis and minor upper respiratory tract symptoms. Influenza virus subtype A(H10) was detected in 2 employees (Arzey et al., 2012; CDC, 2023). That is, this was the second report on the detection of cases of human infection with the A(H10N7) virus.

The influenza A(H10N7) seal epidemic observed in 2014 was also described and was accompanied by a high mortality rate among seals along the north-west coast of Europe and posed a potential risk to human health. The infectious process was limited to the respiratory tract, and the fatal outcome of the infection in the seals was most likely caused by secondary bacterial infections. Infection of ferrets with virus isolates from seals was accompanied by mild clinical signs and inflammation of the respiratory tract that spread from the bronchi to the alveoli and was associated with the expression of the viral antigen exclusively in the respiratory epithelium. The virus was isolated only from the respiratory tract. This indicates that this variant of the virus may have zoonotic potential. The two substitutions made seal's HA A(H10) more stable than avian HA A(H10) and similar to human HA. The authors conclude that the low-pathogenic influenza A(H10N7) virus transmitted from wild birds to seals presents a risk of such cases to mammals and, therefore, to humans (Herfst et al., 2020; van den Brand et al., 2016). In the autumn of 2015, A(H10N7) viruses were isolated from seagulls in Iceland, and genomic analysis showed that they were genetically related to AIVs that had caused outbreaks among seals in Europe a year earlier. Viruses isolated from seagulls showed high binding affinity to human glycan receptors. They could infect ferrets and be transmitted between ferrets both by direct contact and by aerosol. This study showed that avian influenza A(H10) viruses can infect mammals and be transmitted among them without adaptation. That is, the A(H10) virus is a candidate for pandemic influenza and should be monitored in the wild and in animal-human interactions (Guan et al., 2019).

Further molecular genetic studies showed that 3 A(H10N7) strains isolated in 2014 from chickens in live poultry markets in South China, namely *A/chicken/Zhejiang/2C66/2014(H10N7), A/chicken/Zhejiang /2CP2/2014(H10N7),* and *A/chicken/Zhejiang/2CP8/2014(H10N7*), contained the genetic material of circulating AIVs of subtypes A(H10), A(H2), A(H7), and A(H3) at the same time. Reassortant A(H10N7) viruses were minimally pathogenic for chickens and moderately pathogenic for mice. They were able to replicate in mice without prior adaptation.

Discovered new strains may threaten human health in the future if they continue to circulate (Wu et al., 2015).

Influenza virus A(H10N8). The virus belongs to the low pathogenic ones. It was first identified in humans in China in 2013: a 73-year-old woman who visited the live poultry market 4 days before fell ill. Later, 2 more people fell ill. Cases were accompanied by severe pneumonia, respiratory failure, in particular, some ended fatally. When analyzing the results of sequencing the genomes of A(H10N8) strains isolated from humans and poultry from live markets visited by infected people, it is shown that the viruses that infected people came from these markets (Zhang et al., 2014). Although this virus is hypothesized to be a new reassortant among influenza viruses from wild birds and poultry, its evolution to human infection is unknown (Xu et al., 2015). Further studies conducted in 2014 on the circulation of influenza viruses among poultry in the markets suggested that the A(H10N8) virus arose as a result of the recombination of gene segments of viruses of subtypes A(H9) and A(H10) (Hu et al., 2015).

A study conducted to investigate the possibility of infection with this mammalian virus showed the presence of antibodies specific for the influenza A(H10N8) virus in swine herds in southern China. The pathogenicity and transmission of this virus among swine was investigated. Swine were susceptible to the A(H10N8) virus of human origin, which was accompanied by virus shedding, severe tissue damage, and seroconversion. At the same time, infection with the A(H10N8) virus of avian origin resulted only in seroconversion without shedding the virus. This study offers a new perspective on the ecology of influenza A(H10N8) virus and highlights the importance of its epidemiological monitoring in different animal species to prevent and control its spread (Fu et al., 2020).

Zoonotic swine influenza viruses. These viruses belong to 3 subtypes of influenza A viruses and are designated as A(H1N1)v, A(H1N2)v, and A(H3N2)v. However, viruses of these subtypes are not always zoonotic, as they can sometimes be reassortants of seasonal influenza viruses.

Sporadic human cases of swine flu have been reported since the late 1950s. Usually, such patients had direct or indirect contact with pigs. Evidence for human-to-human transmission of swine-origin influenza viruses is very limited, and most cases of swine-to-human transmission have been epidemic dead-end events. One notable exception is the influenza virus A(H1N1) pdm09 (ECDC, 2023, 14 Mar).

Over the past 5 years, 7 cases of influenza caused by viruses of these subtypes were reported on the WHO «Disease Outbreak News» website (Table 1). Among them, 1 was registered in 2018, 1 in 2020, 2 in 2021, 1 in 2022, and 2 in 2023 (Table 1). 1 case was found in the Netherlands, 2 — in the USA, 1 — in Germany, and 3 — in Brazil.

In 2018, a case of influenza was registered in the Netherlands in a 2-year-old child, which was caused by the A(H1N2) virus. The virus turned out to be a reassortant of seasonal influenza viruses. It had NA and non-structural protein (NS) genes from seasonal virus A(H1N1)pdm09 and other genes from A(H3N2) (WHO, 2023). The other 6 cases observed during 2018, 2020, and August 2023 were associated with zoonotic swine viruses. In total, since 2005, there have been 512 cases of zoonotic influenza in humans caused by animal viruses.

The dynamics of human incidence of swine flu and its etiology over the past 6 seasons are given in Table 3 (CDC, 2023). For the period of the 2017/2018—2022/2023 seasons, 49 cases were reported, among which A(H1N2)v viruses (53.1%) prevailed as etiological agents. The largest number of cases was registered in the 2017/2018 season (34.7%) due to 14 cases caused by the A(H1N2)v virus. Further growth occurred in the 2020/2021 and 2021/2022 seasons (28.6% and 24.5% of the total number of cases, respectively).

Regarding the circulation of influenza viruses in swine, the first known introduction of a human influenza virus into the pig population occurred during the Spanish flu pandemic in 1918, and this lineage was named «classic swine» H1N1 (or lineage 1A). These viruses are still circulating among pigs in America and Asia. A virus of the Eurasian lineage 1C is circulating in Europe, which became established after the outbreak that occurred in 1979. Modern swine influenza A(H3N2) viruses in European pigs originate from early pandemic strains of human influenza A(H3N2) and are significantly genetically and antigenically different from modern human influenza viruses. Influenza A(H1N2) viruses were formed in Europe by recombination of swine A(H3N2) viruses and seasonal human A(H1N1) viruses and are still circulating in European pig populations (ECDC, March 14, 2023**).**

When discussing the problem of the further evolution of swine influenza viruses, special attention should be paid to the data of American researchers that the pandemic influenza A(H1N1)(pdm09) virus is able to overcome interspecies barriers with frequent transmissions from humans to pigs. Such cases are observed every year. This can accelerate genetic and antigenic changes, affecting zoonotic risks. During 2010—2020, a correlation was observed between human morbidity and detection of the virus among swine. However, the absence of A(H1N1)(pdm09) circulation in the human population in the 2020—2021 season did not reduce its intensity in swine. During the season 2020—2021, most of the viruses detected in During the season 2020—2021, most of the viruses detected in swine were the result of their transmission from humans to swine in the 2018—2019 and 2019—2020 seasons, indicating their continued persistent circulation among pigs. Swine virus A(H1N1)(pdm09) had variable antigenic reactivity to the vaccine antiserum, but each pigs virus A(H1N1)(pdm09) clade showed significantly reduced cross-reactivity to one or more seasonal human vaccine strains. Also presented is phylogenetic evidence of 17 cases of A(H1N1)(pdm09) transmission from swine to humans between 2010 and 2021, and each of these zoonotic cases was associated with persistent circulation of A(H1N1)(pdm09) among swine. According to the obtained data, the authors conclude that reverse zoonosis and the evolution of A(H1N1)(pdm09) in the process of circulation among swine are a risk for the formation of variants of viruses capable of zoonotic transmission, and this constitutes a potential threat of a pandemic (Markin et al., 2023).

Regular transmission between human and swine influenza A viruses has a strong impact on the evolutionary history of influenza A viruses for both species. The transmission of viruses of different seasonal lineages from humans to swine, with subsequent sustained transmission in the host population and rapid adaptation and evolution, is a major challenge for swine farms. Thus, although only subtypes A(H1N1), A(H1N2), and A(H3N2) are endemic to swine worldwide, great diversity can be found in the

Table 3. **Dynamics of incidence of swine flu in humans and its etiology for the 2017/2018—2022/2023 seasons**

Subtype of influenza A virus	2017/2018	2018/2019	2019/2020	2020/2021	2021/2022	2022/2023	Total
A(H1N1)v	1	1	0	8	0	0	10
A(H1N2)v	14	0	0	4	6	2	26
A(H3N2)v	2	0	1	2	5	1	11
A(H1)v	0	0	0	0	1	0	1
A(H3)v	0	0	0	0	0	1	1
Total	17	1	1	14	12	4	49

HA and neuraminidase (NA) genes, as well as in the other 6 genes of these viruses. These complex processes must be considered on a global scale with regard to the health consequences and prognosis of influenza pandemics (Anderson et al., 2021).

The US Department of Agriculture (USDA) established a swine flu surveillance system in 2009. More than 178,000 samples were tested; more than 9,000 virus isolates and their genetic sequences were obtained; all genetic sequence data are published in NCBI GenBank. So far, a systematic approach has been developed based on the interactive visualization platform octoFLUshow for the analysis and availability of information on the sequencing of influenza A viruses at the level of one gene and the entire genome of the virus (Arendsee et al., 2021).

The swine is also a valuable model for studying the use of monoclonal antibodies against influenza virus as therapy in humans, as well as for monitoring the antigenic drift of influenza viruses in humans to make recommendations for influenza vaccination (Holzer et al., 2020).

Vaccines against zoonotic influenza. As known, every year, the most epidemically significant variants of human influenza A and B viruses are determined for the next flu season that WHO recommends for the production of influenza vaccines for the Northern and Southern Hemispheres. A similar situation is observed for zoonotic influenza viruses. To strengthen the immunogenicity of viruses and their reproductive activity, genetic engineering methods can be used to obtain reassortants.

The selection of candidate vaccine viruses (CVVs), coordinated by WHO, remains an important component of the overall global strategy to prepare for a potential influenza pandemic. To this end, CVVs are being identified that could be quickly used to produce appropriate vaccines in case of an influenza pandemic. The last revision of CVVs for the Northern Hemisphere took place on 02/23/2023. CVVs A(H5N1) currently include 34 strains. Among them, the latest are 3 strains isolated in 2018—2021 (*A/duck/Bangladesh/17D1012/2018* (clade 2.3.2.1a), *A/American region /South Carolina/22-000345-001/2021*- like, and *A/chicken/Ghana/AVL-76321VIR7050- 39/2021*-like (clade 2.3.4.4b)). For the prevention of avian influenza A(H5N6), there are currently 8 CVVs of clade 2.3.4.4 of sublines a, b, d, e, f, g, and h, which were isolated in 2014—2020; for A(H5N8) — 2 CVVs of clade 2.3.4.4 of sublines b and c, isolated in 2014 and 2020. These CVVs were isolated from birds. There are 2 strains — antigenic prototypes of A(H7N1) viruses (*A/mallard/Netherland s/12/2000*, *A/turkey/Italy/3889/99*), A(H7N2) (*A/turkey/Virginia/452 9/2002*, *A/turkey/Virginia/452 9/2002*), A(H7N3) (*A/turkey/Virginia/452 9/2002*, *A/mallard/Netherland s/12/2000*), A(H7N7) (*A/mallard/ Netherland s/12/2000*, *A/mallard/Netherland s/2/2000*), and 1 strain A(H7N4) (*A/chicken/Jiangsu/1/2018-like*).

For the prevention of influenza A(H7N9), 15 CVVs were selected, which, by their antigenic properties, correspond to 6 prototype strains isolated in 2013-2019, and for the prevention of influenza A(H9N2) — 8 (clades Y280/G9 and G1). As for the AIV A(H3N8), which is new to humans, the A/Henan /4-10CNIC/2022 strain is considered an antigenic prototype for the vaccine. 13 prototype strains isolated in 2015—2021 were selected to combat the swine flu pandemic associated with the A(H1) virus, and 5 strains isolated in 2010-2017 were selected for the A(H3N2) virus (WHO, 2023). Thus, the current monitoring of both seasonal and zoonotic influenza allows not only analyzing the current situation and assessing the risks of certain viruses as potential etiological agents of the pandemic but also selecting in advance those strains that can be used for vaccine production in case of immediate threats.

At the end of the work, we would like to provide generalizing figures that were recently provided by the CDC (USA) when comparing

the intensity of epidemic and epizootic processes of influenza caused by zoonotic viruses. For the periods 2005—2012 and 2013—2022, the number of bird flu outbreaks among animals and cases among humans was compared. It was shown that between 2013 and 2022, this number not only increased but was also found over a larger geographic area and among more animals (especially mink). During this time, 34 subtypes of AIVs have been reported, identified in more than 21,000 animal outbreaks and 2,000 human infections. On average 42 countries reported animal outbreaks each year. On average 4 countries reported human infections each year. 16 new subtypes of AIVs were identified; 10 of these were new HPAV subtypes identified in animals, including birds (almost twice as many as during the previous 8 years). Almost 90% of registered outbreaks in animals were caused by 4 HPAV A(H5) subtypes: H5N1 (47%), H5N8 (32%), H5N2 (6%), and H5N6 (4%). 26 countries reported their 1st outbreak of PG influenza in animals. During 2016 - 2022, on average 14% of outbreaks each month occurred among a new category of animals (the largest % was for wild birds — 37%). Such a situation is associated with an increase in poultry production, commercial trade, the role of wild birds, which is due to their periodic migration, including infected birds; a change in migration patterns due to climate change or the involvement of new land for agricultural activity; increasing the efficiency of surveillance. It is emphasized that as outbreaks in animals increase, the risk to humans increases as well, along with the potential for viral reassortment and further transmission of the pathogen. Epidemiological and epizootological surveillance should be comprehensive, covering all subtypes of the virus, providing timely notification of infection in domestic and wild birds, humans, and, ideally, mammals, especially pigs, since pigs can play a decisive role in the formation of a new influenza virus through gene reassortment. It is also necessary to realize that the beginning of persistent transmission of a zoonotic virus among people can become the beginning of an influenza pandemic (CDC, September 7, 2023).

Aware of the existing biological risks regarding potential pandemics, the WHO created the Intergovernmental Negotiating Body Drafting Group to draft and negotiate a WHO convention, agreement or other international instruments on pandemic prevention, preparedness, and response. For now, this body is working on the relevant documents.

Taking into account the existing biological threats, in particular those related to influenza viruses, WHO developed the High-level Implementation Plan III of the Pandemic Influenza Preparedness Framework, which defines a strategy for strengthening global preparedness for pandemic influenza from 2024 to 2030. This Plan takes into account lessons learned during the response to the COVID-19 pandemic, as well as during the implementation of the previous Plan. It is assumed that its implementation will strengthen preparedness for an influenza pandemic at the global, regional, and national levels (WHO, April 19, 2023). This Plan differs from the previous ones in that it focuses on pandemic influenza preparedness policy and planning to further strengthen response capacity; increasing global coverage and institutional capacity of the Global Influenza Surveillance and Response System (eg, expanding genomic sequencing capabilities); the use and expansion of those approaches that were used during the COVID-19 pandemic; supporting those regulatory functions that are necessary to respond to the pandemic, for example in the framework of pharmacological surveillance (procedures established during the COVID-19 pandemic, for emergency situations); providing technical assistance and policy guidance to countries, including those building the capacity for improved vaccine technologies.

Conclusions. Summarizing the data analyzed above regarding the pandemic potential of zoonotic influenza, it should be emphasized that such risks exist constantly. This is confirmed by the tendency to increase outbreaks of avian influenza among birds and mammals and cases among people with the expansion of geographical territories and the involvement of new species and categories of animals. During the last 25 years after the appearance of zoonotic AIV A(H5N1) in 1997, 11 new zoonotic AIVs were discovered in the world. In addition, there was a pandemic caused by the A(H1N1) (pdm09) virus.

Currently, the functioning of the Global System of Epidemiological Surveillance and Response to Influenza allows for identifying influenza viruses new to humans, assessing their adaptation potential to a new species host, assessing evolutionary changes in viruses, selecting candidate virus strains for the production of vaccines in case of aggravation of the epidemic situation and for scheduled vaccination of domestic birds. It should be emphasized that this work must be carried out constantly and within the framework of the concept of «One Health» with the expansion of the territories covered by this supervision.

Acknowledgments. The authors would like to express their gratitude to the National Research Foundation of Ukraine for funding the work carried out under Project No. 2021.01/0006 «Study of circulation of zoonotic influenza A viruses in a natural reservoir, assessment of their epidemic risks and hazards to human health in Ukraine» within the framework of the competition «Science for Security and Sustainable Development of Ukraine».

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Received 30.10.2023

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ЗООНОЗНІ ВІРУСИ ГРИПУ ТА ЇХ РИЗИКИ ДЛЯ ЛЮДЕЙ

На підставі огляду доступних літературних джерел та офіційних повідомлень проаналізовано ситуацію у світі із зоонозного грипу та розглянуто ризики щодо пандемічного потенціалу зоонозних вірусів грипу. Показано, що на тлі генетичного розмаїття вірусів грипу птахів і ссавців та їх здатності до реассортації генів, постійно існує ризик формування пандемічних для людини варіантів вірусів. Такий приклад вже існує, а саме вірус A(H1N1)pdm09, який виявився четвертинним реассортантом вірусів грипу свиней, птахів і людини зі швидкою адаптацією до людської популяції. Після появи у 1997 році зоонозного AIV A(H5N1) у світі виявили нові зоонозні AIVs: A(H9N2) (1998), A(H7N7) (2003), A(H7N3), A(H10N7) (2004), A(H7N9), A(H10N8) (2013), A(H5N6) (2014), A(H7N4) (2018), A(H10N3), A(H5N8) (2021), A(H3N8) (2022). З останніх віруси були ідентифіковані під час пандемії COVID-19. Зоонозні AIVs різних підтипів відрізняються за летальністю для людей (наприклад, для A(H5N1) летальність становить 52 %, а для A(H9N2) — 2.2 %). Вони також можуть відрізнятися за адаптаційним потенціалом до організму ссавців і людини, навіть у межах одного й того ж підтипу. Протягом 2018 — 18.08.2023 рр. у світі зареєстровано 170 випадків грипу у людей, викликаних AIVs, серед яких переважали A(H5N1) (10.6 %) та A(H5N6) (39.4 %). З 2021 року спостерігається їх різке зростання (у 3 рази в порівнянні з 2020 р., та в 5.7 разів у порівнянні з 2019 р.). За період сезонів 2017/2018 — 2022/2023 рр. у світі було повідомлено про 49 випадків свинячого грипу, викликаних вірусами A(H1N1)v, A(H1N2)v та A(H3N2)v. Серед них переважали A(H1N2)v (53.1 %). Існуюча тенденція до зростання кількості спалахів пташиного грипу серед птахів, ссавців та випадків серед людей із розширенням географічних територій та залученням нових видів і категорій тварин може бути пов'язаною зі змінами клімату, збільшенням сільськогосподарських земель та виробництва птиці. Виявленню нових випадків зоонозного грипу серед людей та ідентифікації нових зоонозних вірусів грипу також сприяє підвищення ефективності епідеміологічного нагляду за тяжким респіраторним синдромом, що відбулося на тлі пандемії COVID-19. Зазначене потребує постійного моніторингу циркуляції як зоонозних вірусів грипу, так і вірусів грипу тварин загалом, а також відбору зоонозних вірусів грипу — кандидатів для виробництва вакцин у разі ускладнення епідемічної ситуації.

Ключові слова: *зоонозні віруси грипу, зоонозний грип, нагляд, вакцини проти зоонозного грипу.*