UDC 619:616.98-036.22:578.832.1A:636.4 DOI 10.36016/JVMBBS-2023-9-3-6

RISK OF SWINE INFLUENZA FOR VETERINARY MEDICINE AND HUMAN HEALTH IN UKRAINE

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Summary. The article provides a brief review of the literature on influenza viruses, including their prevalence, classification, pathogenicity, ability to mutate and reassort, and some peculiarities of their biological properties. Special attention is given to swine influenza, since interspecies transmission of influenza viruses between pigs and humans can have serious consequences for both human and veterinary medicine. The results of pilot studies conducted at the NSC 'IECVM' prove the circulation of influenza A viruses among pigs in Ukraine — 324 samples of blood sera from pigs of different age groups from different regions of Ukraine were tested using an ELISA test system, 48 (14.8%) positive samples were found. Seroprevalence reached 100% in some farms and antibodies were detected in animals aged 24–73 days. The prospect of further work is to conduct surveillance studies (serological, molecular biological, virological) of pigs in both large breeding complexes and private households to detect antibodies to influenza A and, based on the results obtained, to draw conclusions about the circulation of influenza A viruses in Ukraine

Keywords: monitoring, swine flu, influenza viruses, enzyme-linked immunosorbent assay

Introduction. Today, the issue of zoonotic pathogens has become particularly relevant following the pandemic of animal-borne coronavirus infections. Of particular concern are avian influenza viruses, swine influenza, and coronaviruses, which can cause severe morbidity and mortality in humans (Coker et al., 2011a; Coker et al., 2011b). According to the WHO, influenza epidemics and pandemics are among the ten worst epidemics and pandemics in recent human history caused by zoonotic viral agents, along with diseases such as Marburg, Ebola, Nipah, MERS, SARS-CoV2. In particular, influenza viruses have caused at least four confirmed pandemics — 1918 (H1N1), 1957 (H2N2), 1968 (H3N2), and 2009 (H1N1) (Piret, and Boivin, 2021; Easterday, 2003; Krueger and Gray, 2012; Scholtissek et al., 1978). Despite its long history, influenza remains one of the most dangerous and unpredictable infectious diseases in the world. To date, influenza A viruses are considered one of the greatest threats for the next global pandemic due to the peculiarities of the pathogen's structure, the large number of natural reservoirs and hosts of the virus, and the ability of the virus to move beyond the natural reservoir and cross the interspecies barrier to infect other species, including humans.

The ecology of influenza A viruses is complex and includes a wide range of host species in birds and mammals, such as human influenza virus (hIV), swine influenza virus (swIV), avian influenza virus (AIV), equine influenza virus (EIV), canine influenza virus (CIV), and bat influenza virus (Muramoto et al., 2013; Shi et al., 2014; Yamayoshi et al., 2016; Suarez, 2016).

The current classification of influenza viruses is based on subtypes of surface glycoproteins, hemagglutinin (HA) and neuraminidase (NA). Currently, there are 18 HA subtypes (H1–H18) and 11 NA subtypes (N1–N9). It is believed that influenza in humans is caused by viruses containing subtypes H1, H2, H3 and N1, N2, although cases of human infection with other influenza virus subtypes are reported. Avian influenza viruses include viruses with subtypes H1 to H16 and N1 to N9, while H17N10 and H18N11 have so far been detected only in bats (Suarez, 2016; Gamblin and Skehel, 2010).

Influenza viruses have a high mutation rate and are constantly changing, which allows them to adapt quickly to environmental changes, such as interspecies transmission. The rapid evolution of influenza viruses is the result of two mechanisms: reassortment (antigenic shift) and point mutations (antigenic drift) (Shao et al., 2017). Both mechanisms play a key role in the emergence of new influenza viruses capable of crossing the host barrier. Once the virus enters the body of a new host, it must adapt and change in order to spread in the new population (Nelson et al., 2014; Lewis et al., 2016; Rajao et al., 2018).

Of all animals and birds, pigs can play a major role in the amplification and creation of new viruses, including influenza (Krueger and Gray, 2012; Mena et al., 2016; Pepin, Miller and Wilber, 2021; Pickering et al., 2021; Wardeh, Baylis and Blagrove, 2021; Hennig et al., 2022).

Transmission between pigs usually occurs through close contact between animals and contaminated objects. Although the severity of the disease is influenced by many factors, including the virus strain, the disease usually begins suddenly as an acute respiratory illness — asymptomatic or mild fever, coughing, sneezing, nasal and ocular discharge, shortness of breath, inactivity and decreased appetite (Rajao et al., 2014; Rajao and Vincent,

2015). There is high herd morbidity (approximately 100%) and usually low mortality (< 1%), but the disease causes high economic losses due to reduced weight gain, especially in young animals (Vincent et al., 2008). The incubation period of the disease is 1–3 days, and recovery begins 4–7 days after disease onset. Virus replication is usually limited to the epithelial cells of the respiratory tract, especially the nasal mucosa, tonsils, trachea, and lungs (Abdelwhab and Mettenleiter, 2023). However, the main concern about swine flu is not so much the economic consequences for the swine industry, but the risks of a new pandemic virus.

Several subtypes of influenza A viruses circulate in swine, including H1N1, H1N2, H3N1, and H3N2 (Lewis et al., 2016; Brockwell-Staats, Webster and Webby, 2009; Chauhan and Gordon, 2020). The classical 'swine' H1N1 virus was first isolated from a pig in the United States in 1930 (Shope, 1931), although an influenza-like disease was clinically recognized in the second half of 1918 during the so-called 'Spanish flu' epidemic (Koen, 1919; Hinshaw et al., 1978). The origin of this pandemic virus — from humans to swine or vice versa — is still unclear (Reid and Taubenberger, 1999; Webster, 1999), but the human virus of 1918 and the swine viruses of 1930 are closely related (Taubenberger et al., 1997; Reid et al., 1999).

Most swine influenza viruses are reassortants, combining genes from swine, avian and human viruses. This confirms the basic dogma that pigs can act as a 'mixing vessel' between human and avian influenza viruses (Wardeh, Baylis and Blagrove, 2021; Hennig et al., 2022; Abdelwhab and Mettenleiter, 2023). This is mainly due to the fact that pigs have both avian and human type receptors (α-*2.3* and α-*2.6*) and can be infected with both avian and human influenza viruses (Nelli et al., 2010). However, it is not entirely clear whether pigs are more susceptible to avian virus infection than humans (Rajao, Vincent and Perez, 2019), although transmission of swIV to poultry, mainly turkeys, has been reported (Choi et al., 2004; Reid et al., 2012; Berhane et al., 2016).

The influenza virus that caused the 1918 pandemic has remained relatively antigenically stable for eight decades without causing major problems for pig farms. The pathogen first entered the European continent in 1976 with exported animals from the United States to Europe and spread rapidly among pigs. And in 1979, a new virus was identified in Europe, which originated from wild ducks and was antigenically different from the 'classic' swine A (H1N1) strain (Zell, Scholtissek and Ludwig, 2012). This 'avian' strain quickly and completely replaced the 'classical' swine influenza viruses circulating on the European continent and also spread in Asia. The classic swine H1N1 and avian H1N1 viruses were the main ones circulating in pigs until the 1990s. In the 1980s, new reassortant H1N2 viruses were discovered in England and then in Europe, which gave rise to new strains of swine influenza virus (Brown et al., 1998).

A new triple reassortant virus with seasonal human H3N2 surface genes emerged in North America in the late 1990s (Olsen, 2002) and subsequently reassortment with classical viruses (H1N1, H1N2) and the creation of a new H3 lineage (H3N2) (Bakre et al., 2021; Karasin et al., 2002; Webby et al., 2004).

In Europe, the H3N2 virus of 'human' origin, derived from the 1968 pandemic virus, was introduced in the 1980s. This virus became widespread after reassorting with the avian H1N1 virus, which was introduced into European pigs in 1979 and remains endemic today (Castrucci et al., 1994; Simon et al., 2014).

Another virus, H1N2, was discovered in 1994 and contained H1, derived from the 1980 seasonal human H1N1 influenza virus, and N2, distinct from the previously isolated H3N2 virus. This virus acquired the internal gene set of the 1979 avian virus through recombination and is now also endemic in Europe (Lewis et al., 2016; Brown et al., 1998; Marozin et al., 2002).

In 2009 these viruses recombined again, this time with influenza A viruses from the Eurasian swine flu lineage. As a result, the strain known as pandemic influenza virus or A/H1N1pdm09 spread rapidly around the world, sickening millions of people (Hennig et al., 2022).

As noted above, interspecies transmission of influenza viruses between pigs and humans is believed to have occurred since the 1918 pandemic and is at least partially responsible for the 2009 swine-origin human influenza, highlighting its zoonotic potential (Hennig et al., 2022; Reid and Taubenberger, 1999; Webster, 1999).

The exchange of viruses between humans and pigs in most cases occurs through close contact, especially on pig farms or slaughterhouses, which is an important risk factor for swine flu infection among pig farm workers. (Borkenhagen et al., 2020; Ma et al., 2018; El Zowalaty et al., 2022; Chauhan and Gordon, 2022). Due to the industrialization of pig production, dense populations of pigs and humans remain in close proximity, and this can increase the risk of transmission of influenza viruses. Zoonotic transmission of H1N1 viruses from pigs has been reported repeatedly in the United States (Hinshaw et al., 1978; Wentworth et al., 1997; Dacso et al., 1984), Europe (Jong et al., 1988; Andersen et al., 2022), Asia (Li et al., 2019; Yang et al., 2022), New Zealand (Eason and Sage, 1980) and Australia (Deng et al., 2020), and in some cases, deaths of infected people have been recorded (Smith et al., 1976; Top and Russell, 1977; Patriarca et al., 1984; Rota et al., 1989; Kimura, Adlakha and Simon, 1998; Wentworth et al., 1994). Thus, from 2010 to 2021, about 700 confirmed cases were reported worldwide, most of which occurred in children or immunocompromised patients (Hennig et al., 2022). Interestingly, transmission of the influenza virus from pig

to human is regularly reported, but the number of human infections is much lower than in pigs (Freidl et al., 2014).

Human influenza is rarely recorded in swine; usually these viruses are reassorted and reappear, retaining only some segments of viral genes of human origin, often with marked genetic differences from the ancestral strain (Nelson et al., 2014; Lewis et al., 2016; Rajao et al., 2018).

It should be noted that since 1918, all pandemic human influenza viruses, with the exception of the 1958 H2N2 virus, have been transmitted by zoonotic means — from humans to swine populations (Hennig et al., 2022). Human influenza viruses have been regularly isolated from swine in the United States, Europe, Asia, and Australia (Castrucci et al., 1994; Deng et al., 2020; Shortridge et al., 1977; Shortridge, Cherry and Kendal, 1979; Nakajima et al., 1982; Katsuda et al., 1995; Nelson et al., 2015a). In addition, anthropozoonotic transmission of seasonal and pandemic influenza viruses to swine has resulted in the creation of a long-term reservoir of zoonotic influenza viruses in swine (Kessler et al., 2021; Glud et al., 2021). In addition to the 'human' subtypes of the virus, the circulation of other subtypes such as H5, H7 and H9 has been reported in pigs (Hennig et al., 2022).

According to some reports (Sikkema et al., 2016), the frequency of subclinical infections in livestock workers ranges from 15% to 40%. And only vaccination programs for workers against seasonal influenza can prevent the occurrence and transmission of infections from animals or vice versa (El Zowalaty et al., 2022).

Swine flu, one of the most prominent zoonotic infections, illustrates the role of trade in its global spread (Nelson et al., 2015b; Gcumisa, Oguttu and Masafu, 2016). In most cases, this is true for regions such as Southeast Asia, where more than 50% of the world's pork production is produced in enterprises of various types (pig farms, households) (Gale, 2017).

Thus, in most cases, small-scale pig farms are characterized by a lack of highly qualified personnel, uncontrolled movement of breeding animals and lack of quarantine measures, intensive and frequent contact between humans and different animal species. All this increases the risk of virus spread between pigs and service personnel, as well as the emergence of new infectious diseases, including zoonotic diseases with pandemic potential (Trevennec et al., 2011; Baudon et al., 2017).

Large industrial swine farms, commonly known as indoor animal feeding operations, are also believed to be sites of origin and transmission of various pathogens, such as porcine reproductive and respiratory syndrome virus, porcine epidemic diarrhea virus, coronavirus acute diarrhea syndrome, and African swine fever (massive outbreak in 2018–2019) (Borkenhagen et al., 2020). For influenza, the importation of livestock in China and other Asian countries has led to the co-circulation of both European (or Eurasian) and North American triple reassortant virus strains containing genes of human origin (Nelson et al., 2015b; Poonsuk et al., 2013).

In addition, reassortant genotypes between these strains containing HA and/or NA genes from human H1N1 and H3N2 viruses have been detected in Asia since the 1960s and have become widespread in swine (Nelson et al., 2014; Liang et al., 2014; Cheung et al., 2023).

Although there have been numerous reports on the prevalence of IAV in organized (commercial) pig farms worldwide during the twentieth century (Chauhan and Gordon, 2020), surveillance of influenza A in pig populations was ignored until the outbreak of the swine flu pandemic in March 2009 (Mena et al., 2016). This appears to have served as a catalyst for surveillance, as most studies were initiated in 2009 (Chumsang et al., 2021, Bravo-Vasquez et al., 2020; Gonzalez-Reiche et al., 2017).

The special role of swine influenza has long been recognized, but these viruses remain highly mobile targets that are notoriously difficult to diagnose due to their remarkable genetic flexibility. One of the main diagnostic tools is molecular genetic testing, which is increasingly replacing traditional laboratory methods. These methods, which use nucleic acid amplification, are characterized by high sensitivity, specificity, and less stringent requirements for the biological material to be tested (El Zowalaty et al., 2022; Chauhan and Gordon, 2022; Gonzalez-Reiche et al., 2017; Mahardika et al., 2018). In most cases, nasal secretions from animals are used as the test sample for molecular studies (Decorte et al., 2015; Janke, 2014). The polymerase chain reaction method provides reliable results in a short period of time, but due to the simultaneous circulation of several influenza virus subtypes, identification errors may occur (Abdelwhab and Mettenleiter, 2023). Consequently, if the virus concentration in samples with these specific subtypes is low, these samples may be misidentified and the subtype with the lower concentration may not be successfully detected (Blair et al., 2019). According to the literature, misidentification also occurs for H3N2 and H1N1 swine subtypes. This is due to the fact that both viruses have genetic similarities with the seasonal human H1N1pdm09 virus (sharing some common gene segments such as M, NS, NP, and HA) (Taylor et al., 2019).

Serologic tests are crucial for the diagnosis of clinical disease, for the immune profile of the herd, for determining the timing of vaccination, for monitoring the effectiveness of vaccination, and for epidemiological studies to identify the dominant virus serotype. Modern serological tests include the hemagglutination inhibition test (HIT) and the enzyme-linked immunosorbent assay (ELISA). ELISA is the most popular serologic test for the diagnosis of swine influenza due to its simplicity, wide range of available tests, low cost and screening nature

(Bravo-Vasquez et al., 2020; Osoro et al., 2019; Jimenez-Bluhm et al., 2018). However, it should be noted that this reaction only detects antibodies to specific subtypes and does not provide complete information on all genotypes circulating in the herd (Chauhan and Gordon, 2022). The ELISA can effectively detect antibodies to swine influenza virus in the serum of animals seven days after exposure to the pathogen or vaccination with a prophylactic vaccine, while the peak may be reached in two to three weeks (Van Reeth, Labarque and Pensaert, 2006; Larsen et al., 2000).

However, it is important to remember that serological tests can produce false-positive or false-negative results, so it is necessary to send material from a large number of animals to obtain reliable test results. In addition, the test systems detect specific antibodies homologous to the antigens in the test system, and all are of little use in detecting antibodies to heterologous influenza viruses.

There is no current information on the epidemiological situation of swine flu in Ukraine. There are only some reports on the presence of antibodies to influenza A virus in wild boars (up to 22.5% of positive samples were detected) (Kovalenko et al., 2017). Therefore, the aim of our study was to perform pilot studies on blood sera of pigs of different age groups from different farms for the presence of antibodies to influenza A viruses.

Materials and methods. The study was conducted at the Department of Poultry Diseases of the NSC 'IECVM'. Blood sera from pigs were collected according to generally accepted methods. For analysis, 324 samples of blood sera from pigs of different ages from farms located in different regions of Ukraine were selected. The sampling scheme is presented in Table 1.

Table 1 — Sampling of blood sera from pigs in different years

Year of sampling	Region	Total number of involved farms	Total number of samples collected
2015 (archive samples)	Poltava	6	60
2021	Poltava	2	119
	Zaporizhzhia	2	14
2023	Khmelnytskyi	1	15
	Dnipropetrovsk	3	75
	Zaporizhzhia	1	15
	Sumy	1	16
	Lviv	1	10
Total			324

The study for the presence of antibodies to influenza viruses was carried out by ELISA using kits manufactured by IDEXX Influenza A Ab Test (USA) and ID Screen® Influenza A Antibody Competition Multi-species (France). All studies were performed according to generally accepted methods in compliance with all biosecurity and biosafety requirements.

Results. The results of serologic testing of samples collected in 2015, 2021, and 2023 are presented in Tables 2–4.

Table 2 — ELISA results for the presence of antibodies to influenza A in pigs from farms in Poltava Region in 2015

No. farm	Number of samples tested	Techno-logical area	Posi-tive	Nega-tive	Sero-preva-lence, %
1	5	sows	0	5	0
	5	fattening	0	5	0
2	10	fattening	0	10	0
	10	sows	3	7	30
3	5	fattening	0	5	0
4	5	fattening	4	1	80
5	7	boars	4	3	57.1
	4	fattening	2	2	50
6	2	sows	0	2	0
	7	fattening	3	5	42.9

Table 2 shows that 30% of the sows from farm 2 were seropositive for influenza A, while no antibodies to this pathogen were detected in the fattening pigs. In the blood sera of fattening pigs from farms 4–6, antibodies were present in 43% to 80% of the animals, and 57.1% of boars from farm 5 were seropositive for the virus.

Table 3 — ELISA results for the presence of antibodies to influenza A in pig blood sera, 2021

No. farm	Number of samples tested	Techno-logical period/ group	Posi-tive	Nega-tive	Sero-preva-lence, %
Poltava Region, XII-139–21					
1	99	fattening	1	98	1
2	10	growing	0	10	0
	10	fattening	0	10	0
Zaporizhzhia Region					
3	5	sows	4	1	80.0
4	9	sows	2	7	22.2

Analyzing the results presented in Table 3, it can be concluded that only one blood serum sample was positive for influenza in the Poltava Region, and 22.2% and 80% of positive samples were found in sows, i. e. animals older than one year, in two farms in the Zaporizhzhia Region.

Table 4 — ELISA results for the presence of antibodies to influenza A in pig blood sera, 2023.

No. farm	Number of samples tested	Technological period/ age of animals	Positive	Negative	Seroprevalence, %
Khmelnytskyi Region					
1	5	24 days	1	4	20
	5	45–49 days	0	5	0
	5	73 days	2	3	40
Dnipropetrovsk Region					
2	5	24 days	0	5	0
	5	45–49 days	0	5	0
	5	73 days	0	5	0
3	5	24 days	0	5	0
	5	45–49 days	0	5	0
	5	73 days	0	5	0
4	5	24 days	2	3	40
	5	45–49 days	3	2	60
	5	73 days	0	5	0
Zaporizhzhia Region					
5	5	24 days	0	5	0
	5	45–49 days	2	3	40
	5	73 days	5	0	100
Sumy Region					
6	16	growing	0	16	0
Lviv Region					
7	10	fattening	10	0	100

As shown in Table 4, 101 samples of pig blood sera from farms in five regions of Ukraine were tested in 2023, and in each region, animals of all ages were found to be positive for influenza A, with seroprevalence ranging from 20 to 100%.

Conclusions. Analyzing the results of our serological studies of unvaccinated pigs of different age groups, it can be stated that most of the animals positive for influenza were older than 3 months (fattening groups, sows, boars, seroprevalence 20–100%). However, antibodies were also detected in blood sera collected in 2023 in animals aged 24–73 days (15 positive samples out of 75 tested), and in the Zaporizhzhia region, 40 and 100% of samples from animals aged 45–49 and 73 days, respectively, were positive.

This is a very high rate of seropositivity to influenza A among pigs. For example, in Asian countries (China, India, Bangladesh, Bhutan, etc.), the average seropositivity from 2009 to 2021 was 18.28% (25.49%, 19.83%, 12.22%, and 7.74%, respectively). A more thorough typing of the positive samples isolated during 2009–2021 using the HIA showed the following proportions: H1N1 (n = 9, 24.32%); pandemic A/H1N1pdm09 (n = 7, 18.92%); H3N2 (n = 6, 16.22%); H5N1 (n = 2, 5.41%); H5N8 (n = 1, 2.7%); H1N2 (n = 1, 2.7%) (Chauhan and Gordon, 2022).

Therefore, domestic pig populations should not be considered as the only or most important reservoir of potentially zoonotic influenza A virus worldwide. Regular and thorough surveillance of pig populations for influenza A virus is essential to monitor the evolution of swIV. The emergence of influenza A virus in pigs during the last human pandemic in 2009 highlighted the major risks for pig populations in which influenza A virus circulates freely and can trigger zoonotic and anthropozoonotic transmission that endangers human health. In addition, understanding the mechanisms associated with host range specificity and adaptation to pigs will allow us to assess the risks associated with the introduction of new viruses into the pig population, and determining the antigenic characteristics of strains circulating in a particular area will ensure the accurate selection of representative vaccine strains to protect the industry.

The prospect of further research is to conduct monitoring studies (serological, molecular biological, virological) of pig herds in both large breeding complexes and private households to detect antibodies to influenza A and, based on the results obtained, to draw conclusions about the circulation of influenza A viruses in Ukraine. The relevance of the planned work is reflected in our pilot serological studies and the high seropositivity of pigs to influenza A (up to 100%).

Acknowledgements. The authors would like to express their gratitude to the National Research Foundation of Ukraine for funding the work carried out under the 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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