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Global avian influenza situation (2019–2022). Host range expansion as evidence of high pathogenicity avian influenza virus evolution

M. V. Zhiltsova, T. P. Akimova, A. V. Varkentin, M. N. Mitrofanova, A. V. Mazneva, V. P. Semakina, E. S. Vystavkina
Federal Centre for Animal Health, Vladimir, Russia

ABSTRACT

High pathogenicity avian influenza has a significant negative impact on poultry farming, international trade and health of wild bird populations, therefore the infection requires the utmost attention of the entire international community. The article investigates the evolutionary and epidemic processes observed in recent years in many countries of the world where avian influenza outbreaks occur; describes the ways of the infection spread; the prevalence of the virus types for the last several years, as well as the expansion of the host range, including among representatives of the *Mammalia* class. The change in the ratio between the virus types starting from 2020, when H5N8 subtype was responsible for the overwhelming number of the disease outbreaks reported, until 2022, when an obvious predominance of H5N1 subtype was detected is demonstrated. A noticeable expansion of the disease-affected areas in Central and South America, the influence of migration, anthropogenic and other factors on influenza spread are highlighted. The conditions facilitating the occurrence of the infection outbreaks affecting mammals, wild animals and livestock, zoo and companion animals are described. Cases of mammals' infection on the North American and Eurasian continents in zoos, nature parks, backyards and fur farms, as a rule, coincide in time with the infection outbreaks in waterfowl populations. The WAHIS data were analyzed and the high ability of the virus to spillover from birds to mammals, such as martens (minks, otters, ferrets, badgers), cats (domestic cats, cougars, leopards, lynxes), pinnipeds (common seals, grey seals), bears (brown, grizzly, American black), bottlenose dolphins, skunks, foxes, opossums, raccoons was demonstrated. Changes in the habitats of both migratory birds and mammals, including due to some human economic activities, add an ecological and urban component to the complex task of the control and prevention of the epidemic, also posing a potential threat to humans.

Keywords: review, avian influenza, mammals, disease situation, expansion of the host range, atypical hosts

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For correspondence: Milena V. Zhiltsova, Cand. Sci. (Veterinary Medicine), Leading Researcher, Information and Analysis Centre, Federal Centre for Animal Health, 600901, Russia, Vladimir, Yur'evets, *e-mail: zhiltsova@arriah.ru.*

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Эпизоотическая ситуация в мире по гриппу птиц (2019–2022 гг.). Расширение спектра хозяев как проявление эволюции вируса высокопатогенного гриппа птиц

М. В. Жильцова, Т. П. Акимова, А. В. Варкентин, М. Н. Митрофанова, А. В. Мазнева, В. П. Семакина, Е. С. Выставкина
ФГБУ «Федеральный центр охраны здоровья животных» (ФГБУ «ВНИИЗЖ»), г. Владимир, Россия

РЕЗЮМЕ

Высокопатогенный грипп птиц оказывает значительное негативное влияние на птицеводство, международную торговлю и здоровье популяций диких птиц, вследствие чего данная инфекция требует самого пристального внимания всего международного сообщества. В статье рассмотрены эволюционные и эпизоотические процессы, наблюдаемые в последние годы при возникновении вспышек гриппа птиц во многих странах мира, описаны пути распространения инфекции, превалентность типов вируса в течение нескольких лет, а также вопросы расширения спектра восприимчивых животных, в том числе среди представителей класса *Mammalia*. Показано изменение соотношения типов вируса с 2020 г., когда подавляющее количество обнаруженных вспышек заболевания приходилось на вирус гриппа подтипа H5N8, до 2022 г., когда было выявлено явное преобладание подтипа H5N1. Отмечено заметное расширение ареала заболевания в Центральной и Южной Америке, влияние миграционных, антропогенных и иных факторов на распространение гриппа. Указаны предпосылки к формированию очагов инфекции с участием млекопитающих: как диких, так и сельскохозяйственных, зоопарковых и животных-компаньонов. Случаи инфицирования млекопитающих на Северо-Американском континенте и в Евразии на территориях зоопарков, природных парков, в домохозяйствах и на зверофермах, как правило, совпадают по времени со вспышками инфекции в популяции водоплавающих птиц. Проведен анализ данных WAHIS и показана высокая способность вируса передаваться от птиц в популяцию млекопитающих, таких как куньи (норки, выдры, хорьки, барсуки), кошачьи (домашние кошки, пумы, леопарды, рыси), ластоногие (обыкновенные тюлени, длинномордые тюлени), медведи (бурые, гризли, американские черные), афалины, скунсы, лисы, опоссумы, еноты. Изменение ареалов обитания как перелетных птиц, так и млекопитающих, в том числе вследствие особенностей хозяйственной деятельности человека, добавляет эколого-урбанистическую составляющую к сложному вопросу борьбы с распространением и предотвращением возникновения эпизоотии, представляющей угрозу в том числе и для человека.

Ключевые слова: обзор, грипп птиц, млекопитающие, эпизоотическая ситуация, расширение спектра хозяев, нетипичные хозяева

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Для корреспонденции: Жильцова Милена Владимировна, канд. вет. наук, ведущий научный сотрудник информационно-аналитического центра ФГБУ «ВНИИЗЖ», 600901, Россия, г. Владимир, мкр. Юрьевец, *e-mail: zhiltsova@arriah.ru.*

INTRODUCTION

High pathogenicity avian influenza (HPAI) has a significant negative impact on poultry farming, international trade and health of wild bird populations, therefore the infection requires the utmost attention of the entire international community.

This disease is caused by viruses divided into multiple subtypes, the genetic characteristics of which can change rapidly over time [1, 2].

Avian influenza viruses (AIVs) are divided into 16 subtypes by hemagglutinin (H1–H16) and into 9 subtypes by neuraminidase (N1–N9) [3]. In addition, new AIV type A subtypes – H17N10 and H18N11 isolated from bats in Guatemala have been identified [4, 5].

Wild birds remain the major reservoir of AI in wild nature, while the virus persistence in the population does not significantly affect the general condition of the hosts [6, 7]. However, the introductions of the virus into unadapted groups of poultry result in severe epidemics with huge economic losses. First of all, this refers to the AIVs of subtypes H5, H7 and H9 [8, 9, 10].

Such a reservoir poses a certain risk, which should be taken into account when animal health measures are planned and implemented [7, 11].

The AI virus is very stable in the environment, can survive for a long time at low temperatures and easily spreads between farms, inside ecosystems, including with fomites (contaminated handling items, equipment). The virus can cross the host-range barrier and infect, although less frequently, animals such as rats, mice, weasels, ferrets, pigs, cats, tigers, dogs and horses. There are known cases of AIV isolation from various mammalian species, including humans [3, 12, 13].

The aim of the study was to analyze the avian influenza evolutionary and epidemic processes in the world in 2019–2022, and these results will provide a more objective picture and will serve the basis for AI monitoring expansion.

MATERIALS AND METHODS

The study was carried out in the Information and Analysis Centre of the Veterinary Surveillance Department at the ARRIAH (Vladimir). The data on AI cases (for example, date, place) were collected from WAHID/WAHIS database of the World Organization for Animal Health (WOAH). Several scientific publications by foreign and domestic authors were also used.

RESULTS AND DISCUSSION

The disease spread. An infected bird sheds the AIV with droppings and through the respiratory tract. The infection is transmitted through direct contact with droppings, through feed and water. The disease has a pronounced seasonality and transboundary nature. Influenza viruses easily spread with migrating birds, creating natural reservoirs of the infection in nesting sites [14, 15, 16].

Poultry is particularly susceptible to the infection. Due to crowding, breed features, technology of intensive poultry farming AI can quickly cause epidemic in the population. In addition, the genetic variability of the

Table 1
Various subtypes of avian influenza virus reported in the world in 2019–2022

Year	Countries	Isolated AIV subtypes
2019	Bhutan, Vietnam, Ghana, Egypt, India, Indonesia, China, Nepal	H5N1
	Egypt, Taiwan	H5N2
	Taiwan	H5N5
	Vietnam, Cambodia, China	H5N6
	Bulgaria, Egypt, Iran, Israel, Kuwait, Namibia, Nigeria, Pakistan, Poland, South Africa	H5N8
	Mexico	H7N3
	China	H7N9
	Bangladesh, Bulgaria, Denmark, Russia	H5 (or not typed)
2020	United Kingdom, Vietnam, Egypt, India, Italy, China, Laos, Nigeria, Netherlands, Senegal	H5N1
	Taiwan	H5N2
	Germany	H5N3
	Belgium, United Kingdom, Germany, Denmark, Italy, Netherlands, Russia, Slovenia, Taiwan, Sweden	H5N5
	Vietnam, China, Philippines	H5N6
	Bulgaria, United Kingdom, Hungary, Germany, Denmark, Egypt, Spain, Italy, Ireland, Iraq, Iran, Israel, Kuwait, Lithuania, Netherlands, Norway, Poland, Russia, Romania, Saudi Arabia, Slovakia, Slovenia, Ukraine, France, Croatia, Czech Republic, Sweden, South Africa, South Korea, Japan	H5N8
	Palestine	H5N9
	Mexico, USA	H7N3
	Australia	H7N7
	Belgium, Germany, Kazakhstan, Ukraine	H5 (or not typed)
2021	Austria, Belgium, Benin, Bosnia and Herzegovina, Hong Kong, United Kingdom, Hungary, Vietnam, Germany, Denmark, Israel, Ireland, Spain, Italy, India, Cambodia, Canada, Latvia, Luxembourg, Mauritania, Mali, Niger, Nigeria, Netherlands, Norway, Poland, Portugal, Russia, Romania, Senegal, Serbia, Slovakia, Slovenia, Taiwan, Togo, Faroe Islands, Finland, France, Croatia, Czech Republic, Sweden, Estonia, South Africa, South Korea, Japan	H5N1
2021	Serbia, Taiwan	H5N2
	United Kingdom, Germany, Denmark, Ireland, Netherlands	H5N3
	Germany, Netherlands, Sweden, Switzerland	H5N4
	Hungary, Germany, Iran, Romania, Russia, Taiwan, Sweden	H5N5
	Austria, Belgium, Vietnam, Denmark, China, Czech Republic	H5N6
	Austria, Algeria, Afghanistan, United Kingdom, Hungary, Vietnam, Germany, Hong Kong, Denmark, India, Iran, Iraq, Spain, Israel, Ireland, Italy, China, Latvia, Lithuania, Netherlands, Norway, Poland, Romania, Serbia, Slovakia, Ukraine, Finland, France, Croatia, Czech Republic, Sweden, Estonia, South Korea, Japan	H5N8
	Mexico	H7N3
	Lithuania	H7N7
	Austria, Belgium, Ghana, Germany, Kazakhstan, Laos, Lesotho, Pakistan, Romania, Russia, Ukraine, Sweden, South Africa	H5 (or not typed)
2022	Albania, Austria, Algeria, Belgium, Hungary, United Kingdom, Vietnam, Germany, Greece, Greenland, Gabon, Guinea, Hong Kong, Honduras, Denmark, Israel, India, Italy, Iceland, Ireland, Spain, Cameroon, Canada, Cyprus, Colombia, Lithuania, Latvia, Luxembourg, Macedonia, Mali, Mexico, Moldova, Nepal, Niger, Namibia, Nigeria, Netherlands, Norway, Portugal, Poland, Romania, Russia, Serbia, Slovakia, Slovenia, USA, Taiwan, Togo, Faroe Islands, Philippines, Finland, France, Croatia, Czech Republic, Montenegro, Chile, Sweden, Switzerland, Ecuador, South Africa, South Korea, Japan	H5N1
	Germany, Poland, Taiwan, South Africa, Japan	H5N2
	USA	H5N4
	Norway, Finland	H5N5
	Albania, Iraq, Israel, Philippines	H5N8
	Mexico	H7N3
	Austria, Belgium, Canada, Kazakhstan, Peru, Japan	H5 (or not typed)

virus contributes to the wide spread of the infection and the emergence of the variants capable of spillover.

Changes in the spectrum of isolated AIVs occur every year. And if in 2020 the overwhelming number of reported outbreaks accounted for AIV H5N8 subtype, then in 2022 there was a clear predominance of H5N1 subtype (Table 1, Fig. 1). In addition, the list of countries that have reported HPAI outbreaks is expanding.

During 2022, new AI outbreaks were reported by Mali, Iceland, Reunion (France). For the first time during

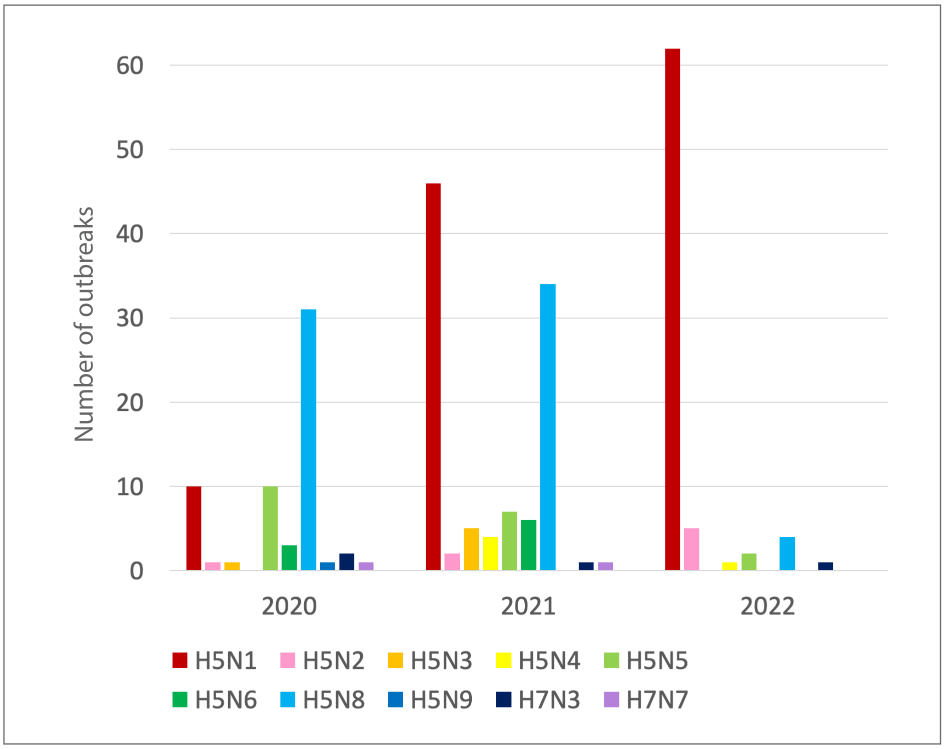

Fig. 1. Prevalence of influenza virus subtypes by year

the observation period (up to January 2023 inclusive), HPAI outbreaks were reported by Colombia, Ecuador, Peru, Venezuela, Panama, Chile and Bolivia [3].

Thus, currently the disease distribution range is expanding in Central and South Americas.

The influence of migration factors on HPAI spread. To date, 14 global migration routes of migratory birds are recognized, 8 of which are more or less related to the Russian territory [17].

Two migration routes seem to be the most relevant on the Eurasian continent for AI possible distribution: Central Asian (the localization of H9 subtype is Pakistan) and East Asian (the localization of H5 subtype is Southeast Asia), since they cross the endemic areas [6].

Overcoming considerable distances, migratory birds are able to introduce AIV to new territories, resting, feeding and nesting sites. By contacting the local fauna, migratory birds spread the virus in new territories and into a new population, maintaining the pathogen circulation and evolving new outbreaks [18].

It should be noted that migration routes are not always clearly defined, however, molecular genetic tests of fecal or cloacal swabs from migratory waterfowl make it possible not only to identify AIV, but also to determine the genetic lineage of the recovered isolate [19].

Synanthropic birds are a kind of the vector of virus transmission from a wild reservoir to susceptible poultry and mammals in the anthropogenic environment. The combination of the described factors has recently led to the occurrence of sporadic cases in animals, not typically affected by this virus.

Potential factors of mammals' infection with HPAI virus. Contact with infected poultry and wild waterfowl, in particular feeding on infected bird meat, is one of the ways of mammals' infection, which creates conditions for AIV spillover [20].

In the wild, the risk of mammals' infection with influenza A viruses is primarily associated with their dietary patterns: hunting or scavenging birds. The role of wild mammals feeding on waterfowl and their carcasses is understudied in influenza epizootics. Contact with synanthropic waterfowl in urban environments can also cause infection of mammalian animals, in particular cats and dogs [21, 22].

Cases of infection with AIV H5N1 in domestic dogs have been published in literature. One of the first cases was reported in 2004 in Thailand and is presumably associated with feeding a dog with infected dead ducks from AI infected areas [23]. In 2009 in Egypt, AIV H5N1 isolates were recovered from nasal swabs collected from donkeys that had been in contact with infected poultry [24]. Studies show that foxes, martens and civets are susceptible to infection with the AIV subtype H5N1 [3, 25, 26, 27].

The susceptibility of Felidae family members to HPAI. *Felidae* family members show a rather high susceptibility to infection with AIV H5N1 subtype [21, 28, 29, 30]. In 2003 and 2004, tigers (*Panthera tigris*) and leopards (*Panthera pardus*) died in Thai zoos due to infection with AIV H5N1 subtype. As a result of the disease outbreak that occurred in the Sriracha Tiger Zoo in October 2004, 147 tigers died or were euthanized [31]. Researchers attribute the infection of big cats to a previous HPAI outbreak in poultry [32, 33, 34].

Testing of isolates recovered from tigers showed that H5N1 is more pathogenic for cats than other AIV subtypes, in addition, changes in the hemagglutinin of these isolates can contribute to an increase in the virus infectivity for mammalian hosts [32, 33].

First domestic cat infections (*Felis catus*) with AIV H5N1 were reported in Thailand in 2004 and coincided in time with outbreaks among poultry [34, 35].

In 2004 HPAI H5N1 outbreak at the Phnom Tamao Wildlife Rescue Centre in Cambodia caused the infection of wild cats of 5 species: lions (*Panthera leo*), Asian golden cats (*Catopuma temminckii*), clouded leopard (*Neofelis nebulosa*), tigers (*Panthera tigris*) and leopards (*Panthera pardus*) [36].

Fatal cases of domestic cat infection with high pathogenicity H5N1 were reported in Iraq in early 2006; it is noted that the infection of animals occurred during the disease outbreak among poultry [37].

One of the first cases of infection with high pathogenicity H5N1of domestic cats in Europe was reported during an influenza outbreak among wild birds on the German island of Rugen in the Baltic Sea in February 2006, where 3 stray cats were found dead [38]. Around the same period, AIV H5N1 isolates were derived from 3 cats kept in a pet shelter in Graz (Austria) after contact with an infected swan in the same shelter. No clinical signs of the disease were found in cats [39]. In 2006, an AIV isolate was recovered from the internal organs of a dead cat in the Republic of Dagestan (Russia) [40].

In early 2013, a case of infection with HPAI virus H5N1 of a 4-month-old Bengal tiger cub in the Jiangsu Province zoo (China) with a lethal outcome was reported [41].

Specialists of the Erasmus University Medical Center (the Netherlands) conducted an experimental infection of European short-haired cats with H5N1 using various methods. Experimental infections with H5N1 virus isolated from a fatal human case confirmed that cats can develop severe clinical signs after intratracheal inoculation. The experiment also confirm that the virus can also be transmitted horizontally from cat to cat [34]. These findings are remarkable, as clinical disease resulting from infection with influenza viruses had not been noticed in cats before [42, 43, 44].

More recent studies have demonstrated that domestic cats can become infected via several routes and shed the virus in aerosols and with faeces, which can facilitate horizontal transmission route [45, 46].

In 2010–2012 in China, serum samples and nasal swabs collected from hundreds of stray cats living in close proximity to poultry farms or poultry markets were tested. As a result, it was determined that some of the animals were infected with AIV H5N1 [47, 48]. In December 2016, HPAI virus was detected in cats in South Korea. Genetic analyses indicated that the feline isolates were similar to AI H5N6 viruses isolated in chicken farms nearby [49].

Isolation of the HPAI virus from mammals in recent years. In 2015, the WOAH was notified about the detection of H5N1 in tigers in the Nanning Zoo (Guangxi, China) [3].

The first documented case of avian influenza (H5N1) infection with characteristic clinical signs in a lion also occurred in Ezhou zoo, Hubei province, China in 2016 [50].

Sporadic cases of AIV infection in marine mammals were reported by the UK Health Security Agency. According to the Agency, AIV H5N8 was isolated from a gray seal (*Halichoerus grypus*) in 2017, and H3N8 from a gray seal and two common seals (*Phoca vitulina*) in 2020 [51].

In November 2020, carcasses of 4 common seals, one gray seal and one red fox were found in Surrey county (England), which were submitted to the laboratory for diagnostic testing. Histopathology of the organ tissues of the fox and one of the seals showed lesions indicative of an acute systemic viral infection. Using virological and molecular biological test methods it was established that animals were infected with AIV H5N8. Two seal carcasses were decomposed so they were disposed of without diagnostics. Since tests for concurrent conditions were not conducted, other factors may have influenced the severity of the disease. There were no previously confirmed cases of highly pathogenic H5N8 infection in foxes [3, 52].

A phylogenetic analysis of H5N1 isolates recovered from 3 red foxes in December 2021 to February 2022 conducted by the Netherlands researchers showed that they were related to HPAI H5N1 clade 2.3.4.4b viruses that are found in wild birds. This suggests that the virus was not transmitted between the foxes [53]. Nevertheless, surveillance in mammals should be expanded to closely monitor the emergence of zoonotic mutations for pandemic preparedness.

The data on the reported AI cases in atypical hosts (mammals) given in Table 2 in section Supplementary files at https://doi.org/10.29326/2304-196X-2023-12-4-293-302, show that recently the AIV has acquired the ability to spillover from birds to mammals, such as mustelids (minks, otters, ferrets, badgers), felines (domestic cats, cougars,

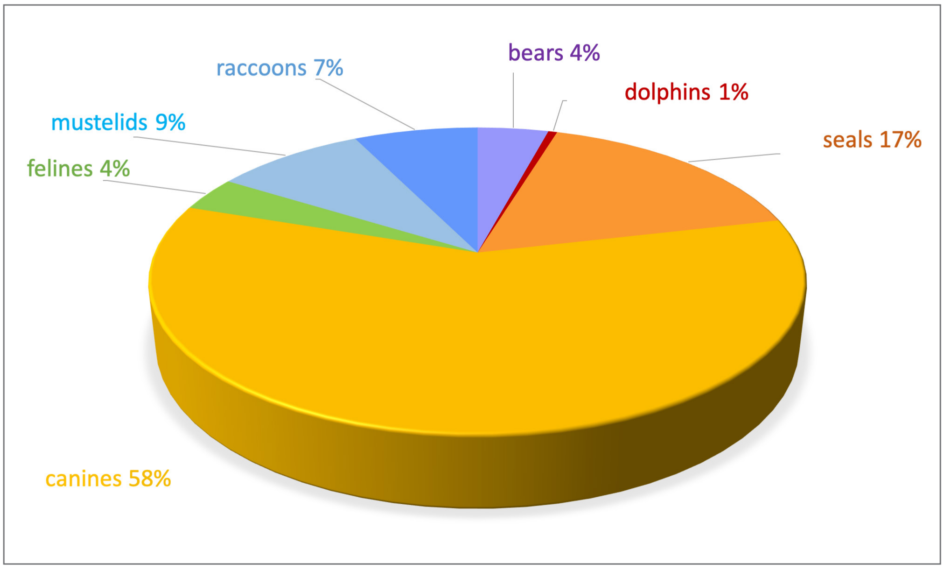

Fig. 2. Ratio of influenza virus infected animals (by families)

leopards, lynxes), pinnipeds (common seals, long-muzzled seals), bears (brown, grizzlies, American black), skunks, bottlenose dolphins, foxes, possums, raccoons (Fig. 2). Cases of infection were reported on the North American and Eurasian continents in zoos, nature parks and households.

As a rule, cases of HPAI infections among mammals coincide in time with outbreaks in waterfowl. The number of reported cases among atypical hosts increased significantly from sporadic cases in 2021 to more than a hundred in 2022. The largest number of such cases was reported in the USA and Canada. France, the United Kingdom, the Netherlands, Denmark and other countries reported AIV infections in mammals (Fig. 3).

Monitoring of the AIV spread in waterfowl, especially beyond the outbreaks, is one of the ways to obtain important epizootological information.

AI transmission from birds to mammals can play an important role in the evolution of new strains of mammalian viruses [57, 58]. Expansion of HPAI distribution area in recent years, an increase in the number of reports about the AIV infection in mammals, as shown in Table 2, a significant increase in the variety of species suffering from pronounced clinical symptoms, suggests a growing zoonotic potential of high pathogenicity H5N1. However, researchers believe that in order to cause a serious pandemic in the human population, the interspecies transmission of influenza viruses is not enough [59].

In the modern urbanization conditions, the number of contacts between migratory and synanthropic birds, domestic animals and humans increases many times, which, in turn, creates provocative conditions both for the virus transmission to atypical hosts and for the occurrence of mutations that carry anthropozoonotic risks (Fig. 4).

Therefore, the WHO Scientific Advisory Group for the Origins of Novel Pathogens (SAGO) is analysing emerging and re-emerging highly dangerous infections, including AI.

CONCLUSION

The comprehensive monitoring of both domestic and wild animals, if there is a possibility of the wild animal contacts with poultry and wild birds (especially waterfowl) is feasible as there is a need for timely measures in order to prevent or reduce the risk of the virus circulation in atypical hosts. The emergence of such a natural reservoir, which includes both typical hosts and mammals, can create conditions for the AIV circulation scheme, which is difficult to monitor.

Currently HPAI affects a wide range of birds and mammals. The disease also attacks rare, endangered species, which may lead to irreparable loss of species diversity.

The change (reduction) of habitats of both migratory birds and mammals due to the expansion of human economic activity, especially on the Eurasian continent, adds an ecological and urban component to AI control challenge and makes control and prevention more complex.

Current complex HPAI situation requires the development and implementation of improved measures, taking into account the latest trends in the disease epizootology.

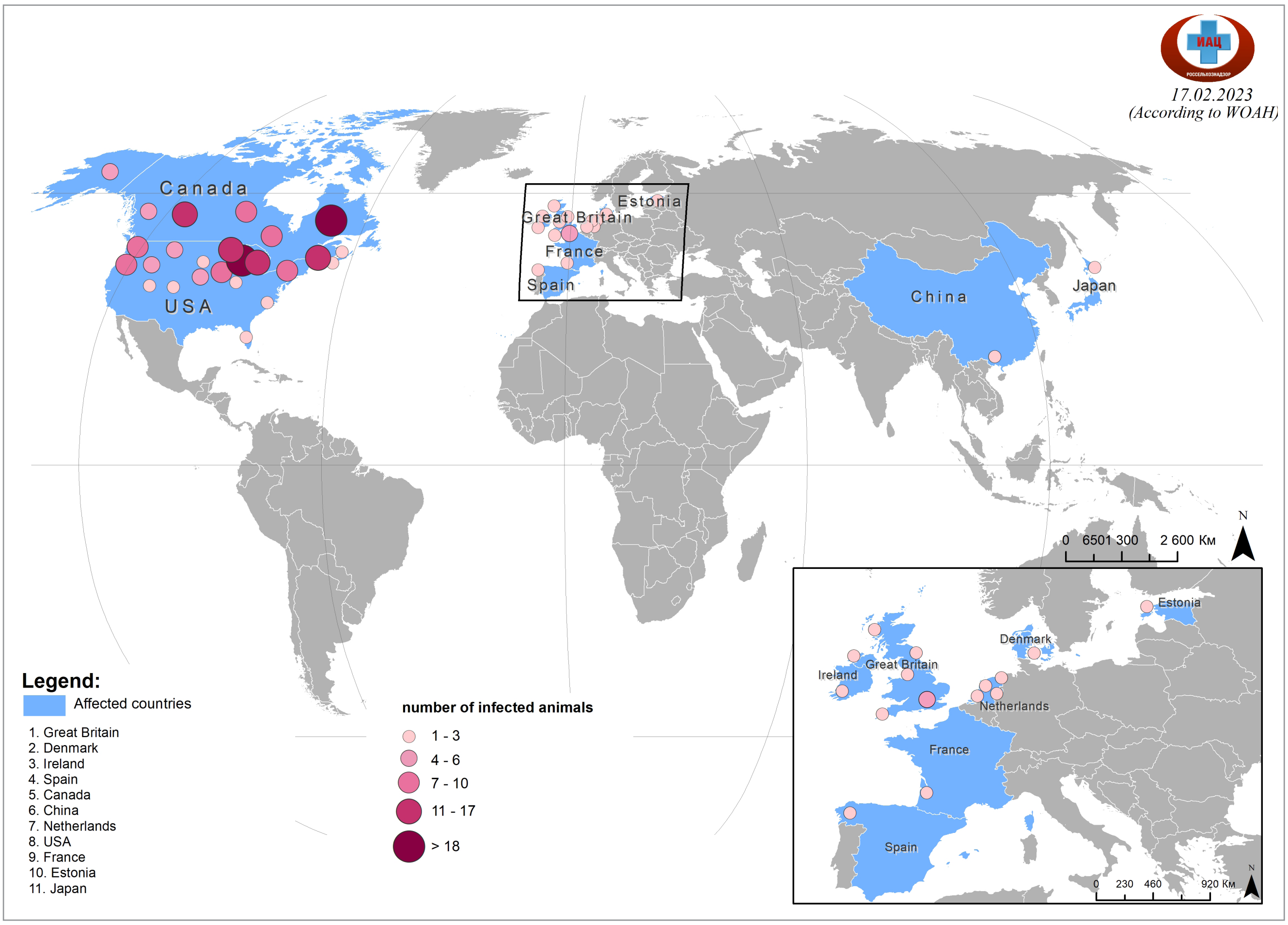

Fig. 3. Occurrence of HPAI infections in mammalians (according to the WOAH data)

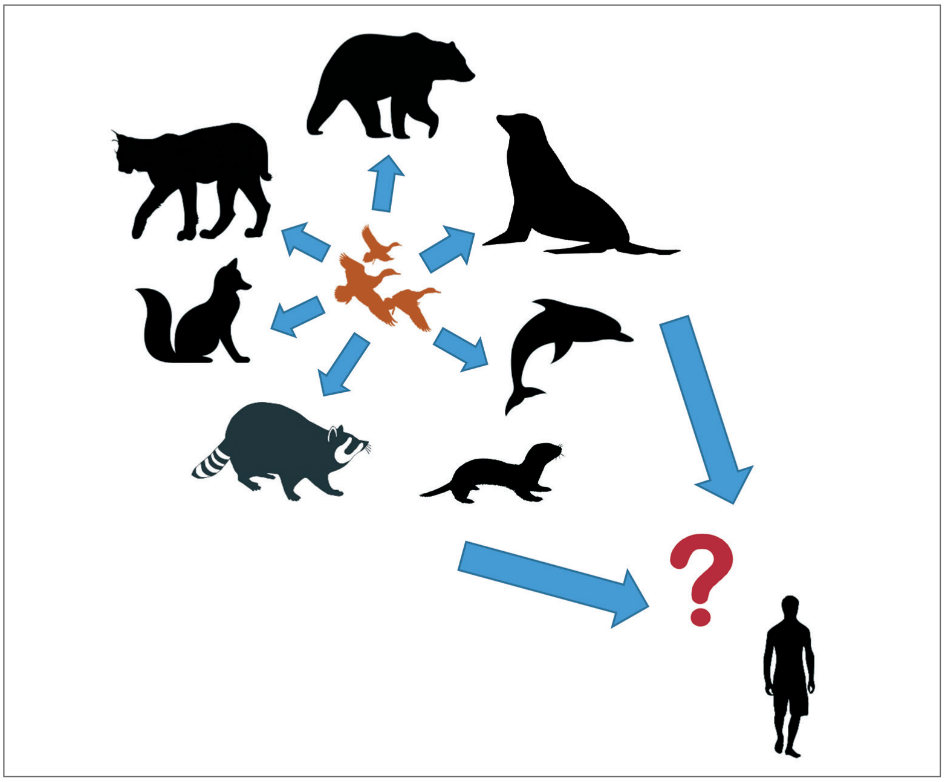

Fig. 4. AIV spillover risks

Currently, there is no sufficient evidence of human infection after contact with infected mammals. The AI virus is able to affect a wide range of avian species and mammals, and thus presents a potential risk to humans.

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INFORMATION ABOUT THE AUTHORS / ИНФОРМАЦИЯ ОБ АВТОРАХ

Milena V. Zhiltsova, Cand. Sci. (Veterinary Medicine), Leading Researcher, Information and Analysis Centre, Federal Centre for Animal Health, Vladimir, Russia;
https://orcid.org/0000-0002-0264-9351, e-mail: zhiltsova@arriah.ru.

Tatyana P. Akimova, Leading Veterinarian, Information and Analysis Centre, Federal Centre for Animal Health, Vladimir, Russia;
https://orcid.org/0000-0003-3502-1146,
e-mail: akimova@arriah.ru.

Andrey V. Varkentin, Cand. Sci. (Veterinary Medicine), Head of Sector, Information and Analysis Centre, Federal Centre for Animal Health, Vladimir, Russia;
https://orcid.org/0000-0002-9732-1083, e-mail: varkentin@arriah.ru.

Mariya N. Mitrofanova, Cand. Sci. (Veterinary Medicine), Junior Researcher, Information and Analysis Centre, Federal Centre for Animal Health, Vladimir, Russia;
https://orcid.org/0000-0003-0126-9653,
e-mail: mitrofanova@arriah.ru.

Anastasia V. Mazneva, Postgraduate Student, Federal Centre for Animal Health, Vladimir, Russia;
https://orcid.org/0000-0002-3442-2004,
e-mail: a.v.mazneva@gmail.com.

Жильцова Милена Владимировна, канд. вет. наук, ведущий научный сотрудник информационно-аналитического центра ФГБУ «ВНИИЗЖ», г. Владимир, Россия,
https://orcid.org/0000-0002-0264-9351, e-mail: zhiltsova@arriah.ru.

Акимова Татьяна Петровна, ведущий ветеринарный врач информационно-аналитического центра ФГБУ «ВНИИЗЖ», г. Владимир, Россия; *https://orcid.org/0000-0003-3502-1146,*
e-mail: akimova@arriah.ru.

Варкентин Андрей Владимирович, канд. вет. наук, заведующий сектором информационно-аналитического центра ФГБУ «ВНИИЗЖ», г. Владимир, Россия;
https://orcid.org/0000-0002-9732-1083, e-mail: varkentin@arriah.ru.

Митрофанова Мария Николаевна, канд. вет. наук, младший научный сотрудник информационно-аналитического центра ФГБУ «ВНИИЗЖ», г. Владимир, Россия;
https://orcid.org/0000-0003-0126-9653,
e-mail: mitrofanova@arriah.ru.

Мазнева Анастасия Владимировна, аспирант ФГБУ «ВНИИЗЖ», г. Владимир, Россия;
https://orcid.org/0000-0002-3442-2004,
e-mail: a.v.mazneva@gmail.com.

Valentina P. Semakina, Head of Sector, Information and Analysis Centre, Federal Centre for Animal Health, Vladimir, Russia; *https://orcid.org/0000-0002-4078-4458,*
e-mail: semakina@arriah.ru.

Evgeniya S. Vystavkina, Leading Specialist, Information and Analysis Centre, Federal Centre for Animal Health, Vladimir, Russia; *e-mail: vistavkina@arriah.ru*.

Семакина Валентина Петровна, заведующий сектором информационно-аналитического центра ФГБУ «ВНИИЗЖ», г. Владимир, Россия; *https://orcid.org/0000-0002-4078-4458,*
e-mail: semakina@arriah.ru.

Выставкина Евгения Сергеевна, ведущий специалист информационно-аналитического центра ФГБУ «ВНИИЗЖ», г. Владимир, Россия; *e-mail: vistavkina@arriah.ru*.