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K. Kh. Zhumatov, A. I. Kydyrmanov, M. Kh. Sayatov

LLP «SPC Microbiology and Virology», Almaty, Kazakhstan.

E-mail: Kainar60@yahoo.com, kydyrmanov@yandex.kz, sayatov37@mail.ru

INFLUENZA A/H9 VIRUSES – IMPORTANT INFECTIOUS PATHOGENS OF WILD BIRDS, MAMMALS AND HUMAN

Abstract. Influenza occupies one of the first places among infectious diseases in terms of the number of biological species involved in the infectious process, and is characterized by global spreading and great economic and social significance. The ubiquitous and uncontrolled circulation of influenza A viruses is primarily due to their unique variability, which is based on both point mutations characteristic of RNA-containing viruses and recombination and reassortment of genes. The review article describes the structural features, sources of isolation and the current classification of influenza pathogens. The main groups of influenza viruses that infect humans, mammals and birds are characterized. The latest literature data on various issues of the structure, ecology, pathogenicity and evolutionary variability of influenza A/H9 viruses of various species origin are summarized. Information is provided on the evolutionary variability of viruses of this group circulating in avifauna, populations of mammals and human. The conclusion is done about the importance of influenza A (H9N2) viruses as a donor in the processes of reassortment and exchanging genetic information between influenza A viruses of various subtypes and the emergence of new, epidemically relevant variants. The need to control circulation of influenza A (H9N2) viruses in order to prevent contact of infected poultry with people and possible appearance of epidemic strains is emphasized.

Key words: influenza virus, A/H9 subtype, bird, genome, variability, phylogenesis, hemagglutinin, antigenic drift.

Influenza occupies one of the first places among infectious diseases in terms of the number of biological species involved in the infectious process, and is characterized by global spreading and great economic and social significance [1].

Influenza viruses belong to the Orthomyxoviridae family, and are divided into genera: Influenza virus A, B, C, D, as well as *Quaranjavirus*, *Thogotovirus* and *Isavirus*; the last two infect leporids and salmon [2]. *Quaranjavirus* representatives circulate both among invertebrates (ticks) and vertebrates (aquatic birds) hosts [3].

Influenza A viruses are widespread in the environment and affect humans, some mammals and birds.

The global and uncontrolled spread of influenza A viruses takes place primarily due to their unique variability, which is based on point mutations that are characteristic of RNA-containing viruses and recombination and reassortment of genes. Their genome consists of eight segments encoding the synthesis of surface glycoproteins HA and neuraminidase (NA), M1 and M2 matrix polypeptides, NS1 and NS2 non-structural proteins, nucleocapsid (NP), polymerases (PB1, PB2, PA) and F2 protein. The most variable structural components of the virion are surface antigens, HA and NA, which play an important role in the initial stages of cell infection, since it is against them that protective antibodies are formed in the host organism.

The classification of influenza A viruses is based on antigenic differences of HA and NA, detected in serological reactions using specific sera, or in BLAST analysis of sequenced genes [4]. The subtype affiliation of all currently isolated influenza A viruses is determined by a combination of known HA and NA subtypes - H1N1, H3N2, H5N1, H7N7, and others, in avifauna, at least 55 variants were isolated [5, 6].

The most recently identified subtypes of NA and NA, are represented in influenza A (H17N10) and A (H18N11) viruses isolated from bats in Central America [7]. Due to the absence of hemagglutinating and neuraminidase activity in these viruses, some authors suggest labeling their surface glycoproteins as “HA-like” and “NA-like”, that is “HL17NL10” and “HL18NL11”, respectively [8].

In the last century, representatives of the H1N1 subtype caused a devastating pandemic of 1918, which killed more than 40 million of people around the world. The pandemics of 1957 (H2N2) and 1968 (H3N2) caused the death of hundreds of thousands of people [9].

The natural reservoir of influenza A viruses are wild birds, mainly related to waterfowl [10, 11]. If the interspecies barrier between birds and mammals is overcome, the influenza A pathogen, after initial adaptation for a rather long period, may acquire the ability to infect a new species, and later circulate in this ecological niche for many decades as an endemic pathogen. Currently such endemic infections include swine, equine and canine influenza, most cases of human influenza. In addition, low pathogenic influenza viruses can cause sporadic, localized epizootics among minks, seals, whales [12]. It should be noted that avian flu is a potentially zoonotic infection that affects poultry and can be transmitted to humans, causing mostly self-limited respiratory diseases. In some cases, they can lead to multiple organ malfunctions resulting in death, especially in immunocompromised patients.

Influenza A(H9N2) virus has been isolated for the first time from wild birds and turkey in USA in 1966 [13]. It is the most propagated subtype among poultry all over the world. During two last decades H9N2 viruses were found in wild birds, poultry, swine, horses, weasels, mink, ferrets and humans [14-19]. In poultry it usually manifests in form of slight clinical signs (e.g. breathing malfunction, drop of egg production and loss of body mass). Lethal cases occur mainly during mixed infections with bacteria and other viruses [20]. The agent also cause temporary immunosuppression which may worsen another coincide or secondary infections [21]. All H9N2 viruses are considered low pathogenic avian influenza viruses based on the lack of mortality in the standardized in vivo pathotyping test in specific pathogen-free (SPF) chickens [22].

In humans, H9N2 most often causes mild respiratory disease, but sometimes lethality cases are observed. Direct transmission of H9N2 from birds to humans has rarely been reported, but serological studies have shown that the prevalence of H9N2 infection in humans is higher than the number of confirmed cases [23-27]. It is noteworthy that all highly pathogenic avian influenza viruses that cause fatal infections in humans (for example, H5N1, H7N9 and H10N8) and registered in the last two decades have acquired gene segments from H9N2 [28-30]. One of the most likely places of origin for such reassortants can be the live poultry markets, which are widespread in the countries of Southeast Asia. For example, M. Hu [31] investigated 618 biological samples collected in 24 markets in Nanchang district (China) in December 2013 and January 2014. Of the 201 samples that were positive in real-time PCR, 20.9% (42/201) contained different HA subtypes. At the same time, in 50% of mixed infections (21/42), the presence of HA subtypes H9 and H10 is shown, with the detection of HA H5 in some cases. According to the authors, this indicates that the H10N8 virus was caused by the reassortment of representatives of the H9 and H10 subtypes. In the same time period, three cases of human infection with the H10N8 virus were reported in Nanchang, one of which was fatal [32].

The evolution of the H9N2 virus in recent decades in poultry has led to diversification into several genotypes. Some have disappeared, while others are still evolving. In 1999, Guan et al. [33] based on the HA gene sequences, grouped H9N2 viruses from Europe, Asia and Africa into several different genotypes represented by their prototype strains: A/quail/Hong Kong/G1/97 (G1-like), A/duck/Hong Kong/Y280/9 (Y280-like), A/chicken/Beijing/1/94 (BJ94-like) and A/chicken/Korea/38349-P96323/96 (Korea-like). Later, Fusaro et al. [34] as a result of phylogenetic analysis of all gene segments of H9N2 viruses isolated in Asia and Europe from 1998 to 2010, revealed four monophyletic groups (A, B, C, D) and the presence of reassortment between them.

The H9N2 virus, along with other avian influenza viruses, is subject to genetic changes affecting the virulence, pathogenicity and specificity of the host. Antigenic drift caused by the absence of the mechanism for correcting viral RNA polymerase in influenza A virus causes high genetic variability due to point mutations in the nucleotide sequence of the genome [35]. These mutations ultimately lead to amino acid substitutions in structural proteins and surface glycoproteins HA and NA are particularly interesting in

this regard. Over time, changes in them are summarized in serologically determined antigenic differences between isolates [42, 36, 37].

At the same time, influenza A virus has a segmented genome, which allows their reassortment in the event that two different viruses infect a single host cell resulting in generation of progeny with genes from both parents. This process is called antigenic shift, as a result of which pathogens of human influenza pandemics can occur. Ultimately, reassortment of gene segments provides the possibility of the rapid emergence of new viruses with unique phenotypic characteristics [42].

It is believed that avian influenza viruses easily infect other organisms, but rarely reproduce well in changing conditions in order to maintain the infection and subsequently become endemic to them [42, 38]. The transition to a new host is facilitated by the fact that they use the surface protein HA to attach to sialic acid as part of the receptor on the surface of the host cell. Sialic acid is the final sugar of *N*- and *O*-linked glycoproteins that are present in most host cell receptors in birds and mammals, which allows viruses to use this universal structure. There are many types of sialic acid, and the relative affinity of HA varies depending on its type, which is one of the factors of host specificity. The majority of influenza A viruses interact with receptors containing α -2,3-linked sialic acid (α -2,3-SA) found in the respiratory and gastrointestinal tracts of birds [35, 42, 43]. In most people, the upper respiratory tract receptors contain α -2,6-SA, with which pathogens adapted to humans form a stronger connection. Many currently circulating isolates of the H9N2 G1 and Y280 lines have mutations that lead to a high affinity for the α -2,6-SA receptor [21, 37, 42, 39]. These changes in HA viruses of the G1 and Y280 lines increase the likelihood of their transmission to humans or other mammals without any additional modification [21]. In turn, the ability of serotype H9N2 viruses to infect people without changing the binding affinity for the receptor increases the likelihood of genetic reassortment between avian and human influenza viruses. In addition, a study of the type and prevalence of various conformations of sialic acid receptors showed that poultry of some species have receptors in the respiratory tract with both α -2,6-SA and α -2,3-SA molecules [42]. These include quails, turkeys and pheasants, which are often found in the live poultry markets, where the H9N2 viruses can thus be transmitted to other species, including humans [40]. Monitoring of avian markets with a high frequency of detection of influenza A viruses of many subtypes is of particular interest, as close contact between people and birds provides ample opportunities for their zoonotic transmission [41].

It was previously shown that influenza A viruses adapted to birds contain glutamine (*Q*) at position 226 of HA, while pathogens that infect humans carry leucine (*L*). Analysis of the amino acid sequence variations of the H9N2 viruses from the GenBank database showed that almost all avian, human and porcine viruses at position 228 contain glycine, which is characteristic of binding to receptors of birds with α -2,3-SA. In position 226, with rare exceptions, only *Q* or *L* was found. Thus, all H9N2 viruses from North America and Korea had *Q*. Representatives of the Y280 and G1 lines possessed *Q* until 2000, but already after 2000 most of them carried *L* at this locus [42]. It is believed that the presence of *L* at position 226 is a factor contributing to the transition of viruses from birds to humans. The reason for the change for *L* in this position in poultry viruses is unclear, but a similar modification is seen in a significant percentage of Chinese avian H7N9 viruses and in an even larger proportion of human H7N9 viruses [43]. The effect of the selective pressure of the human immune system on infectious viruses with an *L* preference in this position is assumed. Thus, 91.3% of the H9N2 isolates isolated from 1998 to 2016 were characterized by the presence of 226L [49].

Another potential source of antigenic drift in avian H9N2 viruses is vaccination, carried out in many countries where this pathogen is endemic in poultry. Vaccine-induced antibodies exert strong immunological pressure, promoting the appearance of various viruses. Thus, vaccination against H9N2 viruses in Korea reduced their genetic diversity, effectively excluding one of the two lines from the circulation (clade A). As a result of this genetically distinct from vaccine strain co-circulating clade B increased its antigenic diversity and became dominant [44].

Reassorting of gene segments is often observed between endemic H9N2 influenza viruses. The mapping of phylogenetic relationships of H9N2 isolates from chickens revealed three main variants. Genotype A, common in the 1990s, was replaced with H better adapted to poultry, and dominating until the mid-2000s. Then in 2007, it was replaced by genotype S viruses, which included G1-like segments of PB2, M and the genetic basis of F/98-like viruses (A/chicken/Shanghai/F/1998) [45].

The genotype S is characterized by increased infectivity, isolation rate, titers, preference for the 2,6-linked sialic acid receptor prevalent in humans and large economic losses, it was he who donated to the internal genes of the H5 and H7 viruses [52, 46-48]. The 2013 A/H7N9 influenza outbreak causative agent in China had all six internal genes derived from the H9N2 viruses, and this new virus line infected both birds and humans [50].

Phylogenetic analysis indicated a distinct genetic diversity of H9N2 viruses and the presence of at least four lines of viruses adapted to domestic birds. When comparing human viruses and poultry viruses, it turned out that all human viruses sequenced belong to the Y280 or G1 lines. No human cases caused by wild bird viruses, or Korean and European lines, have been reported. At the same time, Y280 viruses compared with the G1 line were recorded more often, it is not clear, however, whether this reflected their increased zoonotic potential; perhaps the reason lies in greater isolation rate. The last G1 virus was isolated from humans in 2011, while the Y280 viruses are registered in 2017 [49].

Placed in GenBank and GISAID 24 sequences of the human influenza virus H9N2, which until recently had been available, allowed for comparative genetic analysis. As mentioned earlier, most human viruses contain *L* at position 226 HA, which corresponds to human-adapted viruses. Other adaptation markers are identified in the PB2 and PB1 polymerase genes. The marker in position 627 PB2 is one of the most well characterized; most strains of birds contain glutamic acid in this site, and adapted human viruses - *L*. One of the selective advantages of *L* in this position is increased polymerase activity at low temperature. At a higher temperature typical for birds, glutamic acid at position 627 performs better. Human virus replication mainly occurs in the upper respiratory tract, where the temperature is lower, and *L* provides a more efficient polymerase activity. When analyzing avian and human isolates of the H9N2 influenza virus in PB2 protein, 4 positions were found, where human isolates had the highest percentage of adaptive changes compared to avian viruses. It should be noted that all adaptive mutations characteristic for human viruses are found in at least some avian strains. Over 11% of avian isolates had valine at position 588, which is considered an adaptive amino acid in humans. This change is also associated with polymerase activity [50]. Although the percentage of most of these human-adapted markers appears to be low in viruses in poultry populations, their presence seems to increase the likelihood of viruses that can be transmitted to humans.

In the Republic of Kazakhstan, ecological-virological studies of avifauna were first undertaken in 1979 at the Institute of Microbiology and Virology of the Academy of Sciences of the Kazakh SSR. Since then, up to now, important data have been obtained on various aspects of influenza in wild and domestic birds, and extensive research experience has been gained using the latest molecular genetic research methods. Over the past period, many influenza A viruses have been isolated with various combinations of surface glycoproteins, but no influenza A (H9N2) viruses have been identified [51-57]. In 2014, during the screening of biological materials collected in North-Kazakhstan oblast from wild waterfowl, three viruses of influenza A/H9 were detected by the staff of the laboratory of the ecology of viruses of the LLP «SPC Microbiology and Virology». At present, they are carried out on their full genomic sequencing with a target for a detailed study of phylogenetic characteristics.

In general, literature data indicate the importance of influenza A (H9N2) viruses as a donor in the process of reassorting and exchanging genetic information between influenza A viruses of various subtypes and the emergence of new, epidemically relevant variants. There is an obvious need to limit its distribution among poultry and further transferring to humans and other species, for which vaccination programs, biosafety at poultry farms, and control of live poultry markets are necessary.

Қ. Х. Жұматов, А. И. Қыдырманов, М. Х. Саятов

«Микробиология және вирусология ҒЗО» ЖШС, Алматы, Қазақстан

**А/Н 9 ТОБЫНДАҒЫ ВИРУСТАР – ЖАБАЙЫ ҚҰСТАР,
СҮТҚОРЕКТІЛЕР МЕН АДАМДАРДЫҢ ӨЗЕКТІ ИНФЕКЦИЯЛЫҚ АГЕНТТЕРІ**

Аннотация. Тұмау, экономикалық және әлеуметтік маңызы бар ғаламдық таралумен сипатталатын инфекциялық індеттердің ішінде биологиялық түрінің көптігіне байланысты алғашқы орындардың біріне ие. Тұмау А вирусының жер-жердегі және бақыланбайтын айналымы, ең алдымен олардың РНҚ-бар вирустарға тән нақты мутациялар негізіндегі түрленгіштігінде, сонымен қатар гендердің рекомбинациясы және реас-

сортациясымен түсіндіріледі. Шолымдық мақалада тұмау қоздырғыштарының бөліну көздерімен заманауи жіктелуінің құрылымдық ерекшеліктері сипатталады. Шығу тегі әр-түрлі тұмау А/Н9 вирустарының құрылымы, экологиясы, патогендігі және эволюциялық өзгергіштігі жөнінде әртүрлі сұрақтарды қамтитын әдебиеттердің соңғы деректері қамтылған. Жабайы орнитофаунада, сүтқоректі жануарлар популяциясымен тұрғындар арасында айналымда болатын аталған топтағы вирустардың эволюциялық өзгергіштігі жөнінде мәліметтер келтіріледі. Тұртармақтары әртүрлі тұмау А вирустары және пайда болған жаңа, эпидемиялық өзекті нұсқалардың арасында генетикалық ақпараттың алмасуымен реассортация кезеңіндегі донор ретінде тұмау (H9N2) вирустарының маңыздылығына қорытынды жасалады. Зақымдалған жануарлардың адаммен байланысуын және эпидемиялық штамдардың пайда болу мүмкіндігін болдырмау мақсатында тұмау А (H9N2) вирусының айналымын қадағалау қажеттілігіне мән береді.

Түйін сөздер: тұмау вирусы, А/Н9 тұртармақ, құс, геном, өзгергіштік, филогенез, гемагглютинин, антигендік дрейф.

К. Х. Жуматов, А. И. Кыдырманов, М. Х. Саятов

ТОО «НПЦ микробиологии и вирусологии», Алматы, Казахстан

ВИРУСЫ ГРИППА А/Н9 – АКТУАЛЬНЫЕ ИНФЕКЦИОННЫЕ АГЕНТЫ ДИКИХ ПТИЦ, МЛЕКОПИТАЮЩИХ ЖИВОТНЫХ И ЧЕЛОВЕКА

Аннотация. Грипп занимает одно из первых мест среди инфекционных болезней по количеству биологических видов, вовлекаемых в инфекционный процесс, характеризуется глобальным распространением и большой экономической и социальной значимостью. Повсеместная и неконтролируемая циркуляция вирусом гриппа А объясняется, прежде всего, их уникальной вариабельностью, в основе которой лежат как точечные мутации, характерные для РНК-содержащих вирусов, так и рекомбинации и реассортации генов. В обзорной статье описываются структурные особенности, источники выделения и современная классификация возбудителей гриппа. Обобщены последние данные литературы по различным вопросам строения, экологии, патогенности и эволюционной изменчивости вирусов гриппа А/Н9 различного видового происхождения. Приводятся сведения об эволюционной изменчивости вирусов этой группы циркулирующих в дикой орнитофауне, популяциях млекопитающих животных и среди населения. Делается вывод о важности вирусов гриппа А (H9N2) как донора в процессах реассортации и обмена генетической информацией между возбудителями гриппа А различных подтипов и возникновения новых, эпидемически актуальных вариантов. Подчеркивается необходимость контроля циркуляции вирусов гриппа А (H9N2) с целью предотвращения контактов инфицированного поголовья с людьми и возможного появления эпидемических штаммов.

Ключевые слова: вирус гриппа, подтип А/Н9, птица, геном, изменчивость, филогенез, гемагглютинин, антигенный дрейф.

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