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Pregled | Review

Zoonotic Potential of Currently Circulating Avian Influenza Viruses

Zoonotski potencijal trenutno cirkulirajućih virusa ptičje gripe

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Abstract

Over the past and the current centuries, human influenza pandemics have been attributable to viruses with an avian ancestry. Birds are the main source of influenza A viruses and harbour a variety of antigenic subtypes. Certain avian influenza viruses are capable for cross-species transmission including human infections. Although sustained intrehuman transmission of such viruses has not been documented so far, each human infection with avian influenza viruses provides chances for the virus adaptation towards efficient transmission within human population. Here are reviewed currently circulating avian influenza viruses that are of major significance for public health.

Sažetak

Pandemije humane influence tijekom prošlog i ovog stoljeća pripisuju se virusima ptičjeg podrijetla. Ptice su glavni izvor virusa influence A i domaćini su različitim antigenskim podtipovima. Određeni virusi influence ptica imaju svojstvo prijenosa na različite vrste domaćina uključujući i ljude. Premda održivi interhumani prijenos takvih virusa do sada nije dokumentiran, svaka humana infekcija virusima influence ptica pruža im mogućnost prilagodbe prema učinkovitom prijenosu unutar ljudske populacije. Ovdje su razmotreni trenutno cirkulirajući virusi influence ptica koji su od najveće važnosti za javno zdravstvo.

Introduction

Influenza has been an enormous threat for human health over the history. First records describing a putative influenza-like illness date in 412 BC, in the Hippocrates's „Book of Epidemics" [1]. Today, influenza virus infections in humans are caused by influenza viruses type A, B and C, the first two are associated with significant morbidity and mortality [2]. They are generally manifested as seasonal, zoonotic and pandemic influenza varying from mild, severe to fatal infection. The most threatening influenza infections are the ones caused by zoonotic and/or pandemic strains due to little or no pre-existing specific or cross protective immunity [3]. Although it is not known when the first influenza pandemic occurred, most historians agree that the first pandemic was recognized in 1510 [4]. It is understandable that the subtype of the virus that caused this pandemic is unknown, as well as for almost 30 flu pandemics that occurred over the next three centuries[5]. The first attempts to type the pandemic virus from the end of the 19th century was made using seroepidemiologic data and type A influenza virus of the H3N8 subtype was proposed [6]. In the 20th century several pandemics occurred, all of them caused by type A virus. The most significant pandemic, also known as the Spanish flu, occurred in 1918 and was caused by H1N1 subtype virus [7]. The next pandemic, known as the Asian flu occurred in 1957 and was caused by H2N2 subtype [8]. Already in the next decade (1968), a new pandemic, so called the Hong Kong influenza was caused by H3N2 subtype virus [9]. More recently, H1N1 subtype virus, different from the

Spanish flu virus, caused another pandemic in 2009 [10]. Viruses from the last two pandemics are still circulating in human population causing seasonal influenza A outbreaks. The major pandemics during the past and the current century have been attributable to viruses with an avian ancestry that entered the human population directly or indirectly through intermediate hosts [11]. Unlike others, the 1918 pandemic virus have been wholly derived from avian-like influenza virus from an unknown source [12]. Thus avian influenza (AI) viruses make the foundation of influenza virus infection in humans including previous pandemics, seasonal outbreaks as well as recent human infections caused by zoonotic AI viruses. This paper focuses on AI viruses of major significance for public health.

Ecology and Evolution of Influenza A Viruses

Type A influenza viruses can infect a wide variety of birds and mammals, but the natural hosts and the main source of these viruses are birds from orders Anseriformes (ducks, geese and swans) and Charadriiformes (gulls, waders and terns). Therefore, AI, for most purposes including this article, refers to the influenza A virus. Other species infected with influenza A viruses are considered aberrant hosts. The most common aberrant hosts are terrestrial poultry (chickens and turkeys), domestic mammals (swine and horses) and humans. Distinguishing natural from aberrant hosts is very important in order to understand the ecology of these viruses. The vast majority of influenza A virus is completely adapted to aquatic birds in which the infection does not cause virtually any signs of illness and such viruses in these hosts are in the evolutionary stasis. In contrast, very intense evolution in aberrant hosts is attributed to selection pressure due to the adaptation of these viruses to a new host. Such adaptation can also result in very high virulence for the new host, and sometimes for other species, too[13, 14].

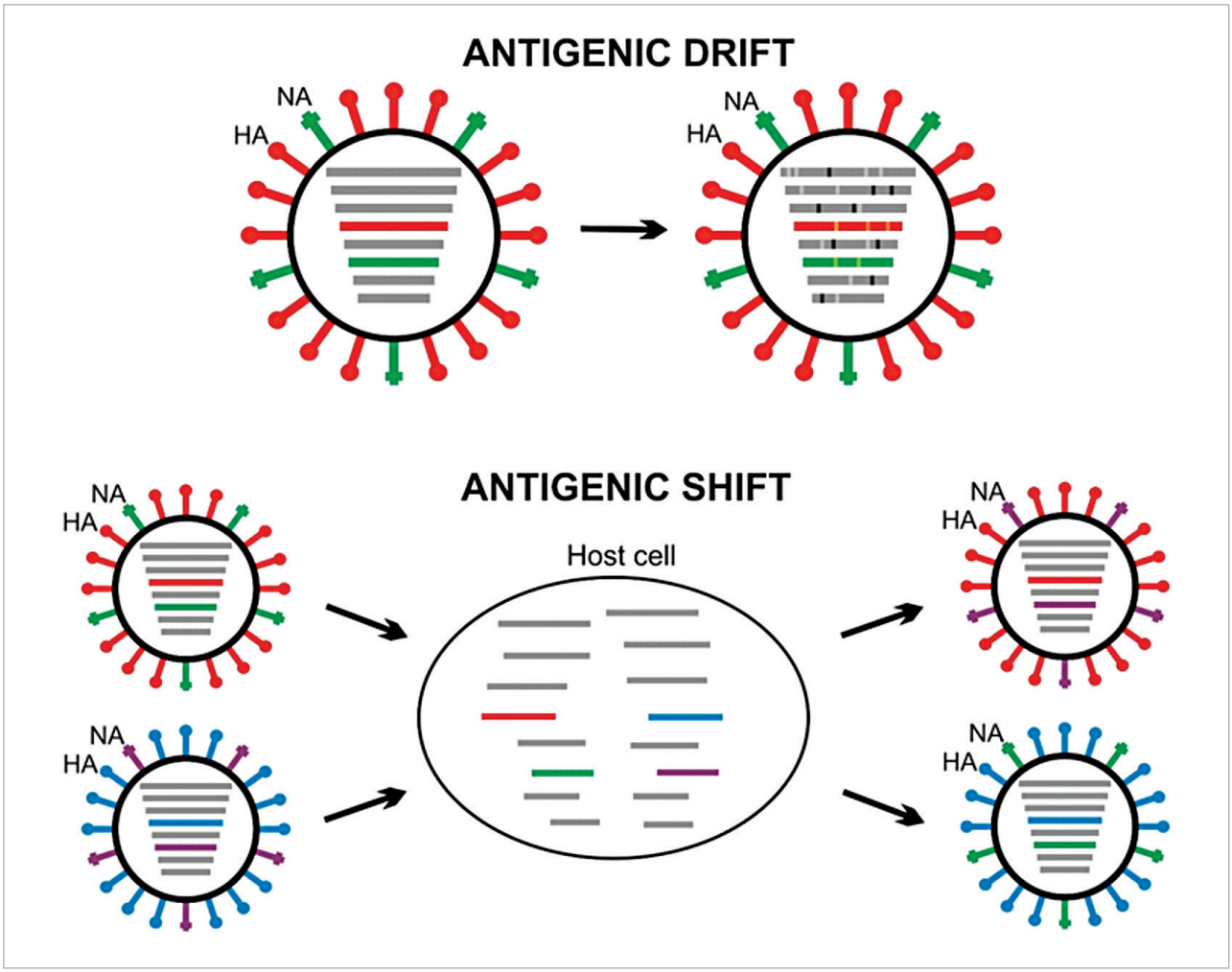
The evolution and diversity of influenza A viruses are driven by two mechanisms (Figure 1). The virus has a negative sense, single-stranded viral RNA genome comprised of eight segments that encode transcripts for 10 essential viral proteins, of which two are surface glycoproteins, hemagglutinin (HA) and neuraminidase (NA)[15]. Accumulation of point mutations in either of the genome segments leading to amino acid changes in the corresponding protein is referred to as antigenic drift, while reassortment (exchange) of virus genome segments from different influenza A viruses during co-infection is referred to as antigenic shift[16]. The point mutation rate is higher in aberrant hosts due to the selection pressure, while the gene segment reassortment is more common in natural hosts due to the abundance of different influenza A viruses. AI viruses can be divided into subgroups according to differences in their surface glycoproteins. So far, 16 HA subtypes (H1 to H16) and nine NA subtypes (N1 to N9) are known and each AI virus has one HA and one NA subtype that can occur in any of the 144 possible combinations (from H1N1 to H16N9). While only a few HA subtypes and several NA subtypes were found in aberrant hosts, all 16 HA and all 9 NA subtypes were isolated from aquatic birds, in most possible combinations. Influenza A viruses are most commonly found in wild ducks in which most HA subtypes are found[14], while subtypes H13 and H16 are found almost exclusively in gulls and related birds[17]. The virus excretion from infected ducks lasts only 2 to 4 weeks, but the virus can be found in their feces in extremely large quantities, even in hundreds of millions of infectious particles per gram of faeces [18]. Avian influenza viruses were isolated from freshly deposited faecal material and from unconcentrated lake water [19]. This provides for the virus to transmit efficiently among gregarious aquatic birds. The virus is further spread to long distances by seasonal bird migrations [20].

Terrestrial poultry are aberrant hosts for influenza A viruses, in which the virus is subjected to strong selection pressure possibly resulting in increased virus pathogenicity, particularly for chickens and turkeys[13, 21]. According to the pathogenicity for chickens and turkeys, influenza A viruses can be divided into two clearly separated groups. Very virulent viruses are multiplied practically in all organic systems and can cause mortality up to 100% causing highly pathogenic AI (HPAI). Such viruses are found only in subgroups H5 and H7, but not all viruses within these two subgroups are necessarily highly pathogenic. The second group includes viruses that cause mild, predominantly respiratory disease, called low-pathogenic AI [14].

Humans are probably the least prone to infection with AI viruses among mentioned aberrant hosts. There are several biological barriers preventing interspecies transmission as well as adaptation to new hosts. One of them seems to be of a particular significance for humans. Influenza A virus attachment to host cellular receptors is mediated by the HA protein, which binds to glycans expressed on the surface of host cells. AI viruses preferentially bind to glycans harbouring sialic acids with α2,3 linkage to galactose. These glycans are abundantly expressed on the surface of avian intestinal and respiratory epithelial cells and they are also present in pig and horse epithelial cells. In contrast, they are poorly expressed in human upper respiratory tract, where glycans harbouring sialic acids with α2,6 linkage to galactose are abundant instead[22].

Figure 1 Evolution and antigenic diversity of influenza A virus is driven by two mechanisms, antigenic drift and antigenic shift. Antigenic drift (above) is the result of accumulation of point mutations in virus genome segments (shown as horizontal bars). Antigenic shift (below) occurs when two or more influenza A viruses of different subtypes infect the same host cell which results in reassortment (exchange) of the genome segments and emergence of new virus subtype. HA represents virus hemagglutinin and NA represents virus neuraminidase.

Slika 1 Evoluciju i antigensku raznolikost virusa influence A pokreću dva mehanizma, antigensko skretanje i antigensko preslagivanje. Antigensko skretanje (gore) rezultat je nakupljanja točkastih mutacija u segmentima genoma virusa (prikazanih horizontalnim linijama). Do antigenskog preslagivanja (dolje) dolazi kada dva ili više virusa influence A različitih podtipova inficiraju istu stanicu domaćina, što rezultira preslagivanjem (razmjenom) segmenata genoma i nastankom novog podtipa virusa. HA predstavlja virusni hemaglutinin, dok NA predstavlja virusnu neuraminidazu.



Nevertheless, it appears that certain AI viruses can cross the biological barriers, attach to human receptors and successfully multiply in humans which means that they posses zoonotic potential.

Human Infections with AI Viruses of Major Significance for Public Health

Although viruses from the several past pandemics have avian ancestry, direct virus transmission from birds to humans was considered rare events of little consequence. Up to 1996, there were only few recorded cases of AI virus isolation from humans, in all cases H7N7 subtype virus [23]. The situation has changed dramatically after 1997, when 18 humans in Hong Kong who were in contact with poultry contracted infection with the zoonotic H5N1 subtype virus and six of them consequently died. This H5N1 is a typical poultry virus belonging to the lineage A/goose/Guangdong/96-like (GD/96) [24]. It is important to emphasise here that lineage GD/96 and its subsequent clades refer exclusively to HA gene, and not to other gene segments. The H5N1 virus spilled-over in 2005

into ecosystem infecting migratory wild birds and spreading across Asia, Europe and Africa during the course of a few months [25-27]. The virus became enzootic and still perpetuates in poultry in several Asian and African countries [28-31]. Recently, from January 1, 2018 up to March 25, 2019, the virus was confirmed in poultry in Bangladesh, Bhutan, Cambodia, China, India, Ivory Coast, Laos, Malaysia, Nepal, Nigeria, Togo and Vietnam [32]. The large number of infected poultry in Asia and Africa provided for local human infections with H5N1 virus. From 2003 to 2017, the laboratories confirmed 860 human cases, out of which 454 (52.8%) of them had fatal outcome. No human cases were reported in 2018 [33]. Detailed numbers of laboratory confirmed human cases by countries and time periods are shown in Table 1.

Since 2003, the GD/96 lineage viruses have been evolving into diverse clades and subclades [34], most of them emerging in Asia. During the evolution of HPAI H5N1 viruses, reassortment events involving the 6 internal gene segments have often been detected, but novel subtypes (i.e., combinations of HPAI H5 with other N subtypes) have rarely been isolated [35]. Unlike other GD/96 clades, a new clade designated 2.3.4.4 [36] comprises of several other H5Nx subtypes. Subsequent reassortment events between viruses harbouring an HA segment originally derived from clade 2.3.4.4 viruses and a range of other avian influenza viruses have generated the H5N2, H5N5, H5N6, and H5N8 subtypes [35]. Similarly to the spread of H5N1 viruses by wild birds in 2005-2006 from Asia to Europe, the Middle East, and Africa during the course of a few months, H5N8 viruses of clade 2.3.4.4 rapidly spread by wild birds from eastern Asia worldwide in 2014-2015 reaching also North America. Subsequent reassortment of these Eurasian origin H5N8 viruses with North American low-pathogenic AI viruses occurred generating intercontinental clade 2.3.4.4 reassortants H5N1 and H5N2 [37]. Second intercontinental spread of this clade reassortant viruses from Asia to Europe and Africa including in most cases subtype H5N8, but also subtype H5N5, occurred in 2016-2017 causing the largest ever recorded epidemic by an HPAI virus in Europe in terms of number of poultry outbreaks, geographical extent and number of dead wild birds[38, 39]. The virus has remained circulating in poultry in Europe at few locations. Nevertheless, H5N8 and related viruses including H5N6 derived from H5N8 virus and European HxN6 (x meaning any H subtype) viruses do not show considerable zoonotic potential with no

Table 1 Cumulative number of confirmed human cases for avian influenza virus H5N1 reported to WHO, 2003-2017[A]

Tablica 1 Kumulativni broj potvrđenih humanih slučajeva influence ptica H5N1 prijavljenih Svjetskoj zdravstvenoj organizaciji (SZO) od 2003. do 2017. godine[A]

Country	2003-2014		2015		2016		2017		Total	
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
Azerbaijan	8	5	-	-	-	-	-	-	8	5
Bangladesh	7	1	1	-	-	-	-	-	8	1
Cambodia	56	37	-	-	-	-	-	-	56	37
Canada	1	1	-	-	-	-	-	-	1	1
China	47	30	6	1	-	-	-	-	53	31
Djibouti	1	-	-	-	-	-	-	-	1	-
Egypt	210	77	136	39	10	3	3	1	359	120
Indonesia	197	165	2	2	-	-	1	1	200	168
Iraq	3	2	-	-	-	-	-	-	3	2
Lao People's Democratic Republic	2	2	-	-	-	-	-	-	2	2
Myanmar	1	-	-	-	-	-	-	-	1	-
Nigeria	1	1	-	-	-	-	-	-	1	1
Pakistan	3	1	-		-	-	-	-	3	1
Thailand	25	17	-	-	-	-	-	-	25	17
Turkey	12	4	-	-	-	-	-	-	12	4
Vietnam	127	64	-	-	-	-	-	-	127	64
Total	**701**	**407**	**145**	**42**	**10**	**3**	**4**	**2**	**860**	**454**

[A]No new cases were reported in 2018

evidence of key mammalian adaptation markers [40-43]. In contrast to the mentioned Asian origin viruses detected in Europe, Far East H5N6 viruses belonging to the same clade (2.3.4.4) cause human infections. Severe infection with avian influenza H5N6 virus in humans was identified first in 2014 in China in patient who presented with fever, severe pneumonia, leucopenia, and lymphopenia, developed septic shock and acute respiratory distress syndrome, and died on day 10 after illness onset [44]. Up to March 14, 2019, a total of 23 laboratory-confirmed cases of human infection with the H5N6 virus, including seven deaths have been reported to WHO [45]. All cases occurred in China between 2014 and 2016. It is interesting that H5N6 virus belonging to the relatively rare clade 2.3.2 of the GD/96 lineage also circulated in poultry in China during this period [46], but no human infections with this virus have been reported so far.

Concurrently with the H5N6 human cases but in a much larger extent, a newly emerged AI virus of the H7N9 subtype was found to infect humans in China. In early 2013, three patients infected with the H7N9 AI virus presented with fever, cough, and dyspnoea. Complications included acute respiratory distress syndrome and multiorgan failure. All three patients died [47]. Up to September 2017 numerous human infections with H7N9 virus occurred in mainland China, resulting in a total of 1,567 laboratory-confirmed cases with 615 (39.2%) fatal outcomes. No new cases of human H7N9 infection were found up to March 14, 2019 [45, 48]. Both, low pathogenic form of this H7N9 virus and its HPAI virus derivate that emerged in poultry in China in early 2017 have been isolated from humans and caused fatal outcomes [49]. Nevertheless, the low pathogenic H7N9 could trigger no illness in birds, which might increase possibility of close contact with virus contaminated poultry [50]. Beside the H7N9 virus, a fatal human infection with related AI virus of H7N4 subtype was reported in China in December 2017 [51]. In addition, two fatal and one severe human infection with AI virus of H10N8 subtype were also reported in China in late 2013 and early 2014 [52].

Another AI virus poses an ongoing concern for human health, namely H9N2 subtype. Since mid 1990s, this virus is widespread in poultry in numerous countries on several continents [53] thus providing abundant chances for human infections. First laboratory confirmed human infections with this virus were reported in 1998 in Hong Kong [54]. Recently, seven human cases were reported in 2018 China and two cases thus far in 2019 [45]. Although human infections with the H9N2 virus do not occur frequently and appear to be mild [55], H9N2 virus has demonstrated significance to public health by donating partial or even whole cassette of internal genes to generate novel human-lethal reassortants like H5N1, H7N9, H10N8 and H5N6 viruses [56].

Conslusions

Apart from human infections with the H5N1 virus which in most instances occurred in Egypt, Indonesia, Vietnam and Cambodia (Table 1), all other human infections with AI viruses occurred exclusively or most frequently in China. Beside the world's largest human population, China hosts a unique ecosystem, comprising large numbers of poultry intermingled with various other animal species which offers an environment for the emergence and spread of novel influenza viruses with the potential for cross-species transmission. In addition, the existence of the large live-poultry markets also increases the possibility of human contact with poultry [57]. Although in most cases infected patients were in contact with infected poultry, there are reports of human infections with no previous contact with poultry, including Canadian resident (Table 1) who returned from China and succumbed due to the infection with H5N1 virus [58]. Such cases raise at least two questions: human-to-human transmission of zoonotic AI viruses and possible infection by food of poultry origin for human consumption. The vast majority of zoonotic events caused by influenza viruses are restricted to sporadic individual cases, without any evidence of sustained human-to-human transmission[59]. Nevertheless, clusters of human infections with AI viruses have occurred on multiple occasions, particularly due to the infection with H7N9 virus. In many situations it is unclear whether these clusters result from person-to-person transmission or exposure to a common infectious source. Limited person-to-person transmission is likely to have occurred, but sustained person-to-person transmission of this virus has not been documented so far [60-62]. However, each human infection with avian influenza virus provides chances for the virus adaptation with subsequent sustained interhuman transmission. The acquisition of human-to-human transmissibility by a zoonotic virus could mark the beginning of a new influenza virus pandemic [59]. Major risk factor for acquiring AI virus infection is intense human exposure to infected poultry like poultry rearing, slaughtering and processing. Food-borne transmission of infection through poultry products may only occur if there is viable virus in the commodity and the concentration of the virus is sufficient to infect the exposed host. Although sufficient viral infectivity to cause interspecies transmissions can be present in poultry commodities from infected birds, consumption of contaminated food has not been sub-

stantiated to cause human infections. Heating poultry products, according to kitchen standards, rapidly inactivates AI virus infectivity and renders fully cooked products safe. For example, complete inactivation of zoonotic H5N1 virus was obtained after exposure at 70°C (1 sec) and at 70°C for 5 seconds for chicken breast and thigh meat respectively. Risks of presence, introduction and transmission of AI viruses through poultry products have been comprehensively reviewed [63-65].

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