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Adequate Monitor of Avian Influenza Viral Infections and Foresight About Possibilities of Its Human Epidemic and Pandemic Infections

Yuji Takemoto

Abstract

Avian influenza viruses are shared among wild birds and sometimes are shed from wild birds to domestic poultry and backyard domestic animals. Usually avian influenza viruses infect wild birds as asymptomatic or low pathogenesis and are stocked in birds, water, and soil. Accumulation of genetic changes of influenza viruses in hosts diversities the pathogenesis to hosts described as highly pathogenic avian influenza viruses and low pathogenic avian influenza viruses. Highly pathogenic avian influenza viruses being categorized among influenza A subtype viruses (H5, H7, H9) and different from low pathogenic avian influenza viruses cause severe illness and sudden increased deaths of wild birds, chicken, or other poultry. These infect from avian to humans. The adequate approaches of information and action for appearance of HPAI and LPAI viral infections in flock may prohibit the outbreak of avian to humans, which are mostly including quarantine of the infected area of the flock from surrounding laboratory tests for HPAI and LPAI viruses in early illness and antiviral treatments in humans.

Keywords: zoonotic infection, antigenic drift, antigenic shift, influenza A virus strain

1. Introduction

There are four types of influenza viruses, types A, B, C, and D, in the world. Influenza virus infection is zoonotic and sometimes restricted to specific species. Influenza A and B viruses mainly cause disease among humans, swine, and avian. Influenza C virus infects humans and swine but does not cause severe disease, and its infection to humans is rarely reported [1]. Influenza D viruses affect swine and cattle and are not known to cause sickness to humans [1]. Influenza B viruses infect humans and avian and cause epidemic in the limiting mild disease [2]. Influenza B virus is concerned about seasonal viral infection but not endemic or pandemic. Influenza A virus is different from other types of influenza viruses about the wide infectious ranges of host and severity of disease. Influenza A viruses are theoretically classified into thousands of different

antigenic subtypes by the combinations of the main viral antigens: hemagglutinin (HA) and neuraminidase (NA) [3]. Recently 18 different HA subtypes and 11 different NA subtypes have been identified [4, 5]. Influenza A viruses are classified from H1N1 to H18N11 and are called as avian influenza virus, swine influenza virus, or other types of animal influenza viruses depending on original infectious host. Humans, swine, and avian are infective host of influenza A virus, but infectious influenza A viral subtypes among intraspecies are restricted by the binding affinity of the HA protein to sialyloligosaccharides (oligosaccharides containing terminal silica acids linked to galactose) on host cell surface glycoprotein or glycolipids [6]. Influenza A viruses cause normally self-limited disease (asymptomatic or mild) and are shared with humans and many different animals. Most subtypes of influenza A viruses are primarily reserved in aquatic birds, are distinct from human influenza A viruses, and do not easily transmit to human due to host species barriers [7]. Zoonotic infection between humans and animals or interspecies of infection of influenza A viruses makes viral evolutions which can help to surmount species barriers [8]. Avian influenza viruses transmit from aquatic birds to poultry and change virus properties and result in change pathogenesis ranging from mild disease to severe disease with high death rates in host species. According to these phenomena, avian influenza viruses cause severe disease and high death rate in host, which are called as highly pathogenic avian influenza (HPAI) viruses, and avian influenza viruses result in mild disease or asymptomatic infection to host, which are called as low pathogenic avian influenza (LPAI) viruses. A virus is defined as HPAI or LPAI by its ability to cause disease and mortality in intravenously inoculated young chickens in the laboratory or by its possession of molecular characteristic features associated with HPAI viruses. Avian, swine, and other zoonotic influenza infections in humans may happen on the condition of the successful transmission with the sufficient contact between donor and recipient species, successful species jumps of influenza viruses, the influenza viral complex adaptations, and achieved sustained transmission in a new species [7]. Those may cause several ranges of disease in humans depending on viral factors and human factors [9]. HPAI virus infections have been monitored from avian to humans and caused the endemic disease of high fatality rate [10]. HPAI viruses may cause pandemic from endemic on the condition of no effective protection for wide shedding of HPAI viruses. Monitoring of disease severity of avian and human influenza A virus infection could prevent the severe damage to the society from the emerging infectious disease of influenza A viruses [9].

2. Evolution of influenza A viruses

2.1 Antigenic drift

Influenza viruses cause annual recurrent epidemics in humans, which approximately result in 3–5 million cases of severe illness and 250,000–500,000 deaths worldwide [11]. Most of these were occurred by influenza A and B viruses. Especially influenza A viruses change viral surface glycoproteins HA and NA by accumulations of point mutations in HA and NA genes and escape from human immunity called as antigenic drift, which may occur as seasonal influenza epidemic. But antigenic drift does not evolve virulence of influenza A viruses which cause severe disease in humans [12]. Seasonal influenza viral infections are limiting disease and mild, which cause severe disease and death by factors of host immune conditions. This does not mean that there is no necessity of treatment of anti-influenza viral therapy

for seasonal influenza infections. The adequate diagnosis and treatment for seasonal influenza infection diminish severe illness and subsequent death from seasonal influenza infections and lead to awareness of emerging infectious disease [13].

2.2 Avian influenza A H5N1 viruses

In 1997 HPAI (H5N1) viruses occurred among wild birds and caused an outbreak in poultry and sporadic human infection in Hong Kong [14]. This was firstly identified as the crossover of avian-human species barrier and resulted in 18 infected individuals and 6 of 18 patients died [15]. Zoonotic infection of avian influenza virus H5N1 has been widely spread from Asia to Europe and Africa, which has been endemic in some countries and caused outbreaks resulting in millions of poultry infections, several hundreds of human infectious cases, and many human deaths since 2003 [16]. Avian influenza virus H5N1 causes a disease which has aggressive symptoms different from a mild disease of seasonal influenza virus infection in humans [9]. HA is a surface viral protein which binds to and uses sialic acid-containing molecules as receptors for viral infection to multiple cells. Avian influenza virus strains circulated in waterfowl contain HAs with preference for binding to sialic acids linked to the rest of the sugar by an α2–3 linkage. In contrast, HAs from human influenza virus strains show enhanced binding to α2–6-linked sialic acids [17]. Seasonal influenza viruses cause symptoms of upper respiratory infection by correlation with an abundance of α2–6-linked sialic acids in the upper respiratory tract of humans [18]. More detailed analysis of H5N1 infection showed an abundance of α2–3-linked sialic acids in the lower respiratory tract of humans, and the explanation of severe disease of the lung was done, as pneumonia and respiratory failure in H5N1 infection [19]. In addition to an abundance of avian influenza viral receptor in lower respiratory tract in humans, the autopsy reports of H5N1-infected patients revealed avian influenza virus infection intra and extra lung concluding the brain, intestine, heart, spleen, lymphoid tissue, kidney, and placenta by applying immunohisto-chemistry (IHC) with monoclonal antibodies to hemagglutinin (HA) and nucleo-capsid protein (NP) and/or in situ hybridization with sense and antisense probes to HA and NP to detect viral antigens and genomic sequences in various organs of H5N1 cases and RT-PCR and nucleic acid sequence-based amplification H5 detection assays [20–25]. HAs with multiple residues at the cleavage site of precursor HAs that can be activated by ubiquitous intracellular proteases may cause systemic infections; on the other hand, HAs with a single arginine residue at the cleavage site of precursor HAs that can only be cleaved by extracellular trypsin-like proteases present in the upper respiratory and gastrointestinal tracts may give rise to local infections [26]. The disease severity in human cases varies from mild to extremely severe; mutations of HA may always be related to the ability of receptor binding but not the virulence of viruses, which imply that there are other factors responsible for the virulence of H5N1 influenza viruses in humans [27]. As the characterization of avian influenza A H5N1, the analysis of H5N1 infections showed the deletion of 19 amino acids of the stalk region in NA protein that cleaves and separates the HA of progeny virions from the sialic acid-containing receptors on the surface of the infected host cells, in which they were generated [14, 28]. This deletion may play a role in the transmission of virus across species [29]. The polymerase complex is composed of three viral polymerase proteins (PB1, PB2, and PA) involved in viral RNA synthesis. In the polymerase complex of avian influenza viruses, glutamic acid to lysine substitution at position 627 of PB2 was isolated but not a prerequisite for high virulence in humans [30]. The 1918 pandemic was called as Spanish flu and proposed that the 1918 virus was not a reassorted virus (like those of the 1957 and 1968 pandemics), but more likely an entirely

avian-like virus that has adapted to humans. But the 1918 influenza virus was analyzed as 10 amino acids change the polymerase complex including the lysine residue at position 627 [31]. These mutations require more investigation for the precursors of a new influenza pandemic. PB1-F2 is a small mitochondrial protein that is encoded on an open reading frame of PB1 [32]. This open reading frame is highly conserved in avian influenza isolates [33]. The reconstructed 1918 influenza virus linked to the PB1-F2 protein and recombinant virus with a single mutation in the PB1-F2 protein [serine (S) instead of asparagine (N) at position 66] of H5N1 (Hk/97) increase viral pathogenicity [34, 35]. PB1-F2 may induce apoptosis of immune cells and an insufficient adaptive immune response [35]. The NS proteins (NS1 and NS2) are viral proteins, and NS1 has multiple functions including splicing and nuclear export of cellular mRNA as well as stimulation of translation [36]. The NS1 protein is crucial for evading the innate immune response of the host by inhibiting the antiviral response mediated by type I interferons [37]. The presence of glutamic acid at position 92 of NS1 has been investigated to be a prerequisite for the resistance to antiviral cytokines considering the results of severe disease induction by inoculation of reassortant influenza virus (H1N1) bearing the NS gene of the H5N1/97 virus to pigs and the lack of glutamic acid at position of the NS1 protein in the recent human and avian isolates [38–41]. Two PDZ ligand (PL) sequence motifs (a Glu-Pro-Glu-Val (EPEV), a Glu-Ser-Glu-Val (ESEV)) were detected in viruses isolated during 1997 but not in viruses after 1997 as a potential codominants of virulence disrupting several PDZ-domain protein-mediated pathways for cell signaling [33].

M1 and M2 are matrix proteins, and M2 is a 97-residue single-pass membrane protein with its N-terminus directed toward the outside of the virus. It determines proton selectivity and unidirectional conductance of the channel by mutagenesis studies [42]. A serine to asparagine substitution at residue 31 of M2 protein is associated with resistance to adamantanes which were used for therapy of influenza A virus infections [43]. On the other hand, M2 protein is suggested to be a candidate for the adaptation of the virus to a new host in addition to PB1-F2 from a study of Thai and Indonesian isolates [43].

2.3 Avian influenza A H7N9 viruses

Avian influenza viruses sometimes infect poultry as LPAI, and there is no concern to LPAI, but even LPAI suddenly caused the sporadic infection among humans which started on February 19, 2013, in Shanghai [44]. There was no epidemic of severe disease in poultry infections with H7N9 before human infections with H7N9. In April 2013, the number of human cases of H7N9 virus infections increased significantly, reaching 125 confirmed cases in China, which was suggested to be derived from contacting with poultry and/or contaminated environments in farmers' markets with live birds [45]. After closure of live birds' markets, the number of new human cases infected with H7N9 declined rapidly. But the second wave of human infections with H7N9 virus started again owing to the lower fall temperature and reopening of poultry markets in the fall of 2013. This wave is characterized by the extensive geographic spread from the province of Eastern China to Southern China and a large number of human infections with H7N9 (440 human infections and 122 associated death of 440 as of May 16, 2014) [46]. For the protection of widespread of H7H9, two strategies composed of suspending farmers' markets with live birds and stopping the transport for trading of live birds carrying the virus were applied by provincial and Chinese authorities [47, 48]. These measures controlled the more spread of H7N9 virus infections in China, but the potential benefits of public health measures should be balanced against the potentially significant societal and economic costs [49]. The lack of protective antibodies in human against

H7N9 virus leads to the result of influenza pandemic in humans, nevertheless of zoonotic infection of poultry to humans [50]. During October 1, 2016–August 7, 2017, the largest fifth epidemic of Asian H7N9 infections since 2013 was reported as 759 human infections including 281 deaths [51]. The total of human infections has reached to 1557 human infections and at least 605 deaths (39%) during March 31, 2013–August 7, 2017 [51]. Fourteen clusters of two or three persons with H7N9 happened during the fifth epidemic Asian H7N9 that was explained in association with wider geographic spread and higher prevalence of Asian virus among poultry and not as a result of any increased incidence of poultry to humans or human-to-human spread [51]. In the genesis of H7N9, H7 of H7N9 is derived from H7N3 viruses isolated among ducks in Eastern China in 2010–2011, and N9 of H7N9 is derived from avian H2N9 and/or H11N9 viruses isolated among wild migratory birds along the East Asian flyway [50, 52]. Both of them are Eurasian lineage of avian viruses, and reassortment of gene (so-called as antigenic shift) may happen and produce the possible precursor of H7N9 virus. Six viral genes except H7 and N9 of H7N9 virus likely originated from chicken H9N2 sub-lineages 1 and 2 circulating in Eastern China [50, 52]. Antigenic shift is suggested to form H7N9 virus during the generation and evolution of viruses. In the analysis of H7N9, viral sequences revealed that H7N9 virus possesses leucine or isoleucine at position 226 of HA which binds to both sialic acid-α2,3-galactose (avian-type receptor) and sialic acid-α2,6-galactose (human -type receptor) [53]. This may mean as the avian virus infection to humans in addition to expression of sialic acid-α2,6-galactose in the upper respiratory tract and sialic acid-α2,3-galactose in the lower respiratory tract in humans [19, 21–25]. According to PB2 protein of H7N9, sequence analysis revealed that many isolated H7N9 viruses encode lysine at position 627 of PB2 [54]. This substitution of glutamic acid (E) to lysine (K) of position 627 of PB2 (E627K mutation) may enable avian viruses to adapt to efficient replication at 33 and 37°C of human temperature lower than original avian host temperature (41°C) [55, 56]. Other mutations of position 627 of PB2 in these viruses have been reported and investigated [56]. The resistant H7N9 variants encoding the R294K mutation in NA that confers resistance to oseltamivir have been detected in patients treated with neuraminidase inhibitors (NAIs). R294K substitution was revealed as multidrug resistance with extreme oseltamivir resistance by the study of using protein- and virus-based assays [57]. On the other hand, K294 mutation of H7N9 infections was found. Compared with H7N9 viruses containing K294 which leads to mild resistance to NAIs, R294K appeared in clinical course under the selective pressure of oseltamivir treatment and conferred not only multidrug resistance to NAIs but also decreases NA activity and impaired virus replication. These phenomena may explain the failure for predominance of R294K-mutated strains of H7N9 in this outbreak. But the drug-resistant mutations should be monitored vigilantly in order to help the most effective drug administration and the prevention of unnecessary loss of human lives in clinical course [57]. Recently LPAI H7N9 viruses have evolved to HPAI viruses and caused the increased morbidity and mortality in poultry, and the same phenomenon has more likely occurred in human infections [51].

2.4 Avian influenza A H7N7 viruses

Outbreaks of HPAI virus infections mostly originate from endemic LPAI viral strains of H5 and H7 subtypes among wild waterfowl. These LPAI virus strains can transmit from waterfowl to poultry and change virulence to HPA virus among poultry [58]. In the Netherlands, an epidemic of HPAI virus H7N7 infection occurred in 2003 that resulted in 255 affected flocks and culling (killing and removing of infected poultry flocks) of 30 million birds [59]. Control measures

were applied to HPAI virus infection in poultry leading to the potential start of human influenza pandemic, such as culling and banning the movement of infected flocks and tracing and screening of the infection which were implemented, followed by preemptive culling of flocks in a 1-km zone around the infected flock. In this HPAI viral epidemic in poultry, 86 poultry workers and 3 household contacts were identified to be affected with H7N7 by RT-PCR, and the main symptom of this infection was conjunctivitis (83/89 persons) and one fatal case happened [60, 61]. Since 2006–2011 LPAI virus infection in the Netherlands (2006) and in Germany (2011) and HPAI virus infection in England (2008) and in Spain (2009), H7N7 viral infections were reported. These show the difficulty in the elimination of epidemic avian influenza viral infection from the endemic avian influenza virus infection among wild waterfowls. As additional measures, vaccination for poultry in outbreaks of H7N7 significantly reduced the excretion of viruses, which may reduce virus spread in infected areas and the risk of human exposure to viruses, in Italy (2000) [62]. Compared with the H7N1 and H7N3 episodes leading no bird to human transmission in Italy, in the genetic analysis of H7N7, HA gene of H7N7 is quite similar to HA genes of H7N1 and H7N3. So other mutations in NA or internal genes of H7N7 virus including E627K in PB2 except HA may determine the capacity to replicate and cause disease in humans. Although H7N7 virus may replicate well in the human cells near the eyes, it may not well replicate in the human upper respiratory tract [61].

2.5 Avian influenza A H9N2 viruses

Influenza virus A H9N2 has been firstly known in 1966 as the infection among turkeys in Wisconsin. Until 1998–1999, influenza H9N2 viruses are less considered to be as zoonotic transmission, although this H9N2 widespread is nearly global including several Asian countries among from wild birds to domestic poultry populations [63]. H9N2 viruses are characterized as LPAI viruses that have caused mild disease which led to decreased egg production and deaths in poultry [64]. In China, natural human infections with H9N2 were firstly reported as seropositive cases in Guangdong province in 1998 and several cases with mild or asymptomatic illness in the South or mainland China and Hong Kong in 1999 [65]. H9N2 LPAI viruses, that were isolated from an infected human in Pakistan in 2012–2015 and in Northern China in 2017, have an identical amino acid residue leucine at 226 in the receptor binding site of HA, the C-terminus of PDZ ligand motif in NS1 (KSEI), NP (E372D), and L55F in the M2 protein that are mammalian host-specific markers [64, 66]. Avian influenza H9N2 viral infections have been globally distributed as mild and asymptomatic infection in humans, poultry, pet birds, and other domestic animals and may trigger weak immune responses and production of low titer of antibody to H9N2 in humans [63, 66]. These were inducted as infections from poultry to humans directly or indirectly, but not as human-to-human transmission [63, 66]. Low rates of influenza A H9N2 viral infection in poultry-exposed individuals may cause an epidemic with a longer duration or a greater magnitude than if the virus was introduced to a completely unexposed population [67]. H9N2 also demonstrates its potential to efficient transmission from avian hosts and sharing genetic materials (e.g., internal genes) with other viruses as appearance of H7N9 and H10N8 [68, 69].

2.6 Other avian viruses in human infections: H10N8, H5N6, H7N2, H7N3, H6N1, and H10N7

In China in 2013, human infection of avian influenza A H10N8 virus was firstly reported as severe illness which resulted in death within 9 days of clinical course [69].

This strain is different from others isolated from poultry and wild birds and reassortant of H9N2 containing genetic markers for mammalian adaptation and virulence in HA (A135T, S138A), M1 (N30D, T215A), NS1 (P42S), and PB2 (E627K). This virus was sensitive to neuraminidase inhibitors (NAIs) [69].

In China in 2014, human infection of avian influenza virus was caused by H5N6 HPAI virus following the epidemic infections of many birds' death [70]. Until 2017, a total of 16 human cases infected with avian influenza H5N6 and 11 fatal cases of 16 cases (an overall CFR of 69%) were reported [71]. Thirteen of 16 cases had exposure to live poultry or live poultry markets (LPMs). Avian influenza H5N6 viruses belonged to HA H5 genetic clade 2.3.4.4 have evolved from H5N1 and H9N2 viruses [72], and similar H5 clade A (H5N6) viruses have been detected in wild birds and poultry in China, Japan, Lao People's Democratic Republic, Myanmar, the Republic of Korea, and Vietnam [73]. Analyses of poultry and environmental samples indicate that the different avian influenza A H5N6 virus genotypes may vary by geographic regions as HPAI viruses or LPAI viruses [73].

In the United States of America (USA) in 2016, avian influenza A H7N2 infected one human after an outbreak of infection among cats in an animal shelter in New York City. This person's infection was associated with close contact with sick cats affected with H7N2-isolated virus and no widespread to any other persons [74]. Avian influenza H7N2 viral infection to humans has been reported as the result of prolonged long contact with infected birds since 2002 in the USA. But the screening of more than 350 people with exposure to infected cats during this outbreak appeared no more human infection except one, and the risk posed by this virus to the public was thought to be low. Isolated H7N2 viruses in the USA are characterized as LPAI virus but have increased binding to sialic acid-α2,6-galactose receptor and reduced binding to sialic acid-α2,3-galactose receptor which has the possibility of human-to-human infection [75].

In Canada in 2004, a two-time outbreak of avian influenza A H7N3 viral infection happened in one farm: the first was characterized as LPAI viral infection which resulted in 8–16 deaths/day among 9200 chickens in a barn, and the second was detected as HPAI viral infection which resulted in 2000 deaths in 2 days among 9030 chickens in an adjacent barn [76]. After the outbreaks of LPAI and HPAI virus infections, the examination of testing for H7N3 among approximately 2000 poultry farm workers and 650 workers assisted with outbreak management and control revealed 57 suspected and/or confirmed as avian influenza infections [76]. Only two confirmed patients with avian influenza A H7N3 virus had conjunctivitis and mild influenza-like illness cases infected with avian influenza A H7N7 virus in the Netherlands.

In Taiwan in 2013, a human infection with avian influenza A H6N1 was recognized as mild pneumonia and quick improvement by treated oseltamivir. A 20-year-old woman works at a breakfast shop and had not been exposed to poultry or birds and no travel to China. Investigation of 36 close contacts with her cleared no positive tests for avian influenza A H6N1, and two poultry farms within 1 km from the woman's house were investigated as the results of no H6N1 virus infection [77]. Avian influenza A H6N1 virus strain commonly circulates in domestic birds in Taiwan, and this infection happened to be found in the alert of a Taiwanese traveler's infection with epidemic avian influenza H7N9 virus in China in 2013. Genetic and structural analysis of isolated H6N1 virus reveals that a single nucleotide substitution resulting in a change from Gly to Asp at position 225 of HA (G225D) leads to direct interaction of Asp225 with the penultimate of Gal of the human-type receptor and the stabilized binding to human receptor [78]. E627K mutation in PB2 is well known to human adaptation of avian influenza viruses but is not present in avian and human isolates.

In Australia in 2010, an outbreak of LPAI H10N7 viruses was identified as 10–25 bird's deaths for 8–14 days, a 15% decrease of egg production, and no respiratory signs in affected flocks. Two of seven abattoirs who had conjunctivitis and minor upper respiratory tract symptoms were identified to be infected by H10N7 virus [79]. In Australia in 2010, surveillance for H10N7 viruses showed small numbers of wild waterfowl on the affected site and no infection of H10 subtypes in poultry around 2 km of affected farms.

2.7 Other strains of avian influenza viruses.

In addition to avian influenza strains of poultry to human infections, epidemics of avian influenza A strains are reported: H5N2, H5N5, and H5N8 viruses as HPAI viruses and H3N8, H6N6, H10N4, H10N5, H11N2, and H7N8 as occasional infection to mammals.

3. Transmission of species

3.1 Genes' transport of wild birds to poultry by antigenic shift

As above, many avian influenza reasssortant viruses have emerged during viral transmission from wild birds (donor spices) to poultry (recipient species). LPAI viruses from wild birds have been reasserted with other influenza virus strains of poultry and changed virulence in poultry. If LPAI viruses could not adapt to new host of poultry, they would die out. LPAI viruses have been environmentally sustained by close contact to LPAI viruses among wild birds when avian influenza A virus infections happened in endemic countries. Host species barriers do not mean simply the biological barriers [7]. Biological barriers between wild birds and poultry are almost the same in concerning about influenza binding receptor in cell membrane ($\alpha2$–3-linked sialic acids) and replication condition in host temperature [19, 53]. In addition to biological barriers, interspecific interactions between wild birds (donor) and poultry (recipient), interactions between avian influenza viruses and poultry (recipient), and interactions among individuals of poultry (recipient) are considered as environmental barriers [7]. In consequence of surmounting these barriers, LPAI viruses have been sustained by the successful onward adaptation to new hosts like H7N7 viruses, H9N2 viruses and H7N9 viruses in the present [47, 59, 64]. If humans have been in close contact to poultry affected with LPAI viruses, asymptomatic or mild illness of avian influenza A virus infections would appear in humans but rarely leads to fatal disease [45, 46]. LPAI viruses suddenly have changed virulence to HPAI viruses and caused severe disease and deaths among poultry like the emergence of H5N1 virus being in consequent to human epidemic [14]. Increased virulence from LPAI to HPAI following antigenic shift could not be predicted before the happening. Avian influenza A viruses need to acquire the abilities to transmit to new host species and replicate effectively in new host before an epidemic or pandemic [7]. Antigenic shift in avian viruses has transmitted the abilities of transferring from poultry to humans and replicating progeny in humans by accumulated mutations in HA, NA, PB2, NS1, etc. but has not transmitted the abilities of transferring from human to human [28–38].

3.2 Possibility of intermediate hosts or mixing vessels for the generation for pandemic influenza viruses

Avian has $\alpha2$–3-linked sialic acids, human has $\alpha2$–6-linked sialic acids, and swine has both types of receptor for HA of influenza A viruses [80]. These enable
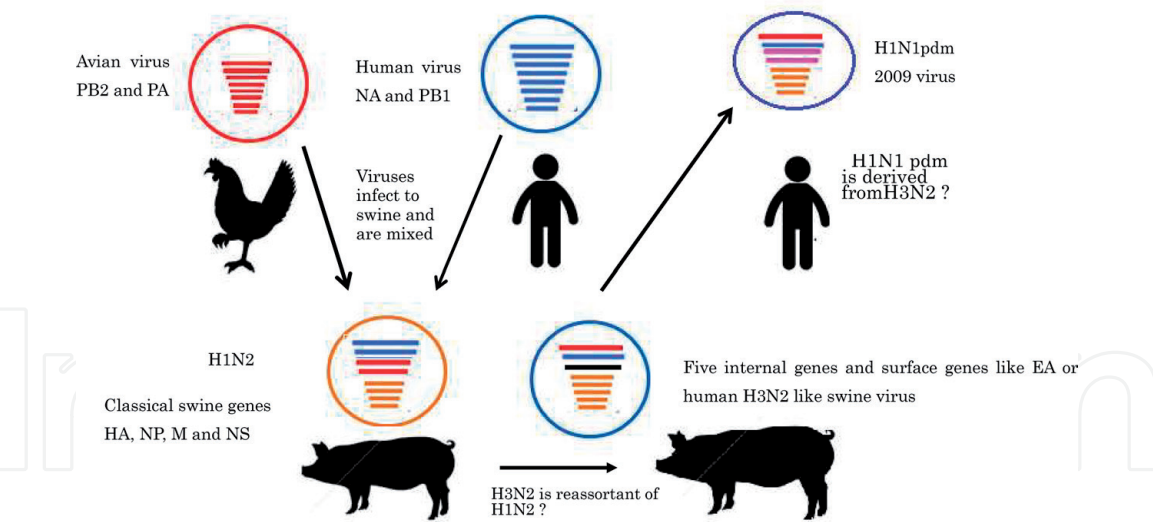
Figure 1.
Reassortant H1N2 influenza viruses and H1N1 pdm 2009 in swine.

pigs to be susceptible to both human and avian influenza viruses. If a human influenza A virus infection and an avian influenza A virus infection happened simultaneously in swine, antigenic shift may produce new pandemic viruses which can be transmitted easily from person to person among human population with little or no immune response to them. In China, avian-like H1N1 and novel reassortant H1N2 influenza viruses from pigs were reported [81]. The swine H1N1 virus (A/swine/Zhejiang/1/07) was close to avian-like H1N1 viruses which is seemed to be derived from the European swine H1N1 viruses, and the two H1N2 viruses (A/swine/Shanghai/1/07 and A/swine/Guangxi/13/06) were novel reassortant H1N2 influenza viruses containing genes from the classical swine (HA, NP, M, and NS), human (NA and PB1), and avian (PB2 and PA) lineage, which indicated that the reassortment of influenza viruses happened among humans, avian, and swine and the generation of new viruses was produced in swine [81]. In the analysis of influenza virus H1N1 pdm in 2009, the main persistent pdm/09-origin reassortant forms had at least five pdm/09-origin internal genes, and their surface genes were primarily of European avian-like (EA) or human H3N2-like swine influenza virus [82] (**Figure 1**). The monitor for a new pandemic virus is necessary to monitor and survey the epidemic infection in swine, in addition to monitoring of endemic LPAI infections among wild birds and poultry, epidemic LPAI and HPAI infections among wilds birds and poultry, and the following human infections by LPAI and HPAI viruses.

4. Systemic monitor and approach for a new information of epidemic and pandemic infections

Avian influenza viral infections are wide ranges of mammalians, and it is not enough to monitor avian, swine, and humans for covering all types of avian influenza virus infection because of the rare case appearance of the LPAI outbreak in cats in the USA [74]. The World Health Organization (WHO) continuously monitors avian and other zoonotic influenza viruses closely through its Global Influenza Surveillance and Response System (GISRS) (http://www.who.int/influenza/gisrslaboratory/en/). From this site, necessary information about occurrence of outbreaks, conditions, widespread of infections, etc. can be investigated and gathered. But insufficient monitor for zoonotic influenza infections as potential to

the human pandemic is reinforced by the information from the collaboration with the World Organization for Animal Health (OIE) (www.oie,int/) and the Food and Agriculture Organization (FAO) (www.fao.org/home/en/). In each country, the national disease center monitors its own country and internationally collaborates with the WHO. Monitoring reinforces the environmental barriers by noticing abnormal wild birds' deaths in a province to the provincial and national authorities in an early stage of an endemic. Following this information, provincial authorities would start to investigate etiology of birds' deaths and any other birds' deaths around this area and water pollution by avian influenza viruses in ponds if avian influenza viruses caused birds' deaths. Environmental barriers have three steps which are composed of a first step of transmission from waterfowl to poultry, a second step of transmission of individuals among poultry, and a third step of transmission from poultry to humans (**Figure 2**). When a first step of environmental barrier from wild birds to poultry is surmounted by avian influenza viruses, two patterns of damage in poultry (asymptomatic/mild disease or severe disease/ deaths) are recognized. It is very difficult to detect early and diagnose asymptomatic infections in poultry, but any changes in poultry including coughing and decrease numbers of egg production should not be missed. Recently rapid influenza diagnostic tests (RIDTs) are available in testing for avian influenza viruses (H5, H7, and H9), but other RIDTs for detection of more HA subtypes are desirable to be developed in demand [83]. If any doubt for avian influenza infection, RIDTs are recommended to be applied immediately within the limits of lower sensitivity than RT-PCR and other methods. A combination of RIDTs (infection of avian influenza viruses), RT-PCR (viral genes sequence and subtypes), HA inhibition test (viral subtype), ELISA (all subtypes of avian influenza viruses and widespread of viral infection), and the inoculation of isolated viruses to chicken (identification of viral pathogeny) would be adapted without any time consumption for diagnosis. These tests may provide an initial measure and further measures for control of an endemic, epidemic, and a potential pandemic infection of avian viruses. A second step of environmental barrier is reinforced by using the following measures: isolation of birds from the others, the use of personal protection equipment (PPEs)
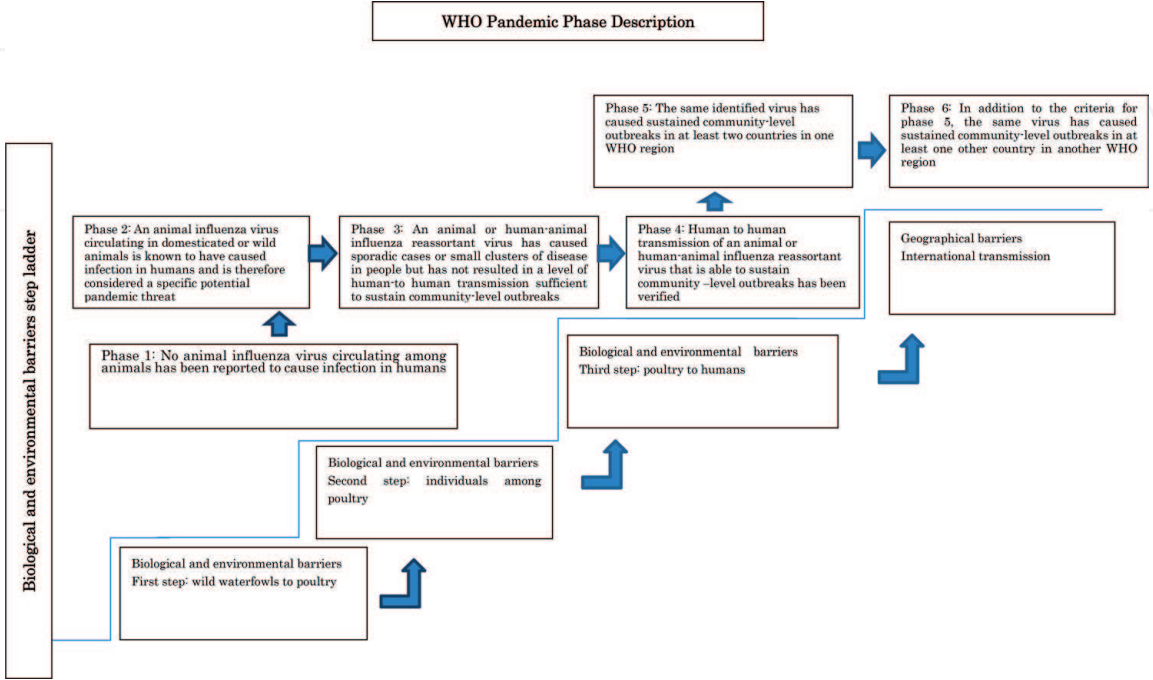

Figure 2.
Comparison WHO Pandemic Phase and biological and environmental barriers step ladder.

by farm workers, and culling the affected birds. But widespread of avian viral infections among poultry is not necessary for a long time. So it is desirable to diagnose avian viral infection in the shortest time since the first notification of disease by these diagnostic tests. Vaccination of poultry has been applied for the prevention from economic damage of culling and a potential pandemic, as biological barriers [84]. But vaccines of animals for avian viral infections would be desired to high efficacy and prevalence use in the areas. Considering the negative effect for the difficulty of conducting surveillance for persistence of the virus after vaccination or insufficient immune response in birds leading to the latent viral infection in poultry, vaccination should carefully be adapted as one component of control measures [84]. Control strategies and measures including technical guidelines for pandemic potential are available from FAO and OIE [84, 85]. It is emphasized that the surveillance standards and methodology are necessary for calling rapid response for containment or mitigation of emerging infectious disease of avian influenza but not a system for rapid detection of emerging novel influenza strains or outbreaks of disease [85]. Sentinel surveillance is desired to protect poultry and humans from the threat of epidemic and/or pandemic potential in the prevalence of avian viruses among wild birds and poultry. Collapse of a third step of environmental barrier is recognized as human infection with avian influenza viruses. This condition is called as pandemic phase 2 in the WHO pandemic phase descriptions [86] (**Figure 2**). Human infection primarily may appear in direct or indirect exposure to infected live or dead poultry or contaminated environments, such as live bird markets. And human infection also may appear concerning slaughtering, de-feathering, handling carcasses of infected poultry, and preparing poultry for consumption, especially in household settings [87]. Surveillance of avian viral infections in these persons will be done by applying combinations of diagnostic methods as soon as possible from the onset of the first poultry infections. Consumption of prepared poultry and raw egg dishes has been reported to be linked with the infection of H5N1 human cases [87]. The virus is inactivated at temperatures (at least 70°C the center of the product) in conventional cooking, and consumption of properly cooked poultry and eggs should be recommended [88]. Although human-to-human transmission of avian influenza viruses may occur in the close and/or prolonged contact with the patients, there has been no sustained human-to-human transmission of these viruses identified [89]. But in North America in 2009, influenza A (H1N1) pdm 009 virus originated from swine influenza viruses surmounted biological barriers. It took only a few months to amount to a total number of 73 affected countries and more than 26,000 laboratory-confirmed infected cases from the first case in Mexico in February of 2009 which is called as pandemic phase 6 (**Figure 2**) [90]. These suggested how fast infections had been spread in the world and how difficult to control the widespread of emerging infectious disease (EID) after the new emerging avian influenza virus had obtained the capacity of the interhuman transmission. In this phase, therapy for patients and adaptation of control measures for pandemic were necessary. Antiviral drugs for influenza viral infections except adamantanes are effective for avian influenza infections in the early stage of infection for the decrease of mortality rate [91]. Administration of neuraminidase inhibitors (NAIs) to infected persons within 48 hours of onset would be recommended, and isolation of infected people from the public would be important in a limited term. Recently baloxavir marboxil that prevents replication by inhibiting the cap-dependent endonuclease activity of the viral polymerase and is effective for seasonal influenza and avian influenza virus infections is available in Japan [92]. In addition to NAIs, it may be one of the powerful tools as antiviral therapy. In the pre-pandemic stage to the pandemic stage, network information and control measures from the national disease center, the Global Influenza Surveillance Network (GISN), Global Outbreak

and Alert Network (GOARN), and the original network for influenza viral infection in province. In usual diagnosis and treatment of influenza viral infection, RIDTs are a useful step-up strategy for the treatment of influenza viral infections regardless of limiting sensitivity. RIDTs for seasonal influenza viral infection can only detect A type and/or B type of viral HA but not subtypes of HA strains. But these tests recognize human and avian influenza viral strains (H1N1, H2N3, H3N8, H4N6, H5N2, H6N2, H7N7, H8N4, H9N2, H10N7, H11N6, H12N6, H13N6, H14N5, H15N8, H16N3, H5N1, H5N6, H5N8, H7N1, N7 N7, and H7N9) as influenza type A viral infections (Tauns Inc.). By the results of these tests, and then if an antiviral therapy for influenza viral infection would be applied to patients. And then if an antiviral therapy is judged as not to be effective by the evaluation for the time of alleviation of fever in humans with influenza viral infections, further investigation for complications of viral infections, a new emerging viral infection using RIDTs for HA sub-strains, RT-PCR and/or viral cell culture, or mutant viruses resistant to antiviral drugs [13, 93]. In the pandemic phases 4–6, there may be many patients with influenza viral infection. It is very important to minimize the severe fatal disease from HPAI or LPAI infections and to select and send the patients with severe disease to the hospitals under the capacities for admission effectively by the triage between mild disease and severe disease. So this system may enable an early intervention of viral infections within 48 hours from onset and less numbers of patients with severe disease. It is not necessary to divide seasonal viral infection treatment from LPAI infection treatment except the necessity of special training and area for protection of widespread of EID using PPE. Like in the case with LPAI H6N1 virus in Taiwan [77], LPAI viral infections may be treated without identification in the circumstance of avian viral widespread among domestic birds. As one of the control points for pandemic preparedness, the candidate pandemic vaccine is desired and planned to be developed for prophylaxis and the most effective one of the control measures. The WHO has developed the influenza candidate vaccine viruses (CVVs) which are planned to be supplied to national authorities for pilot lot vaccine production, clinical trials, and other pandemic preparedness purposes based on their assessment of public health risk and need (contact at gisrs-whohq@who.int) [94]. Effective pandemic vaccines may be the most powerful measures for pandemic.

5. Conclusion

Pandemic is unpredictable, but sequential efforts to minimize and diminish the vulnerability of human public health from pandemic are desired in the world. Sentinel monitor and surveillance for endemic, epidemic, and pandemic potential is necessary for early detection of pandemic potential and pandemic preparedness planning. Sequential diagnosis and treatment from seasonal to avian influenza viruses adapted to humans may be beneficial in decreasing the risk of pandemic potential derived from zoonotic influenza virus infections. Preparations and developments of the candidate vaccine for the information following sequential monitor are necessary for the control against the phase of pre-pandemic and pandemic by avian influenza virus. The diverse of using several types of anti-influenza viral drugs with single and/or combinations for the pandemic infections would be desirable to be established as possible as a pandemic will be happen.

Conflict of interests

The author has no competing interests to declare.

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