Chapter 1

Introductory Chapter: Human Influenza A Virus Infection - Global Prevalence, Prevention, Therapeutics, and Challenges

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1. Introduction

Influenza virus is a perpetual economic burden that causes a significant morbidity and mortality rate in humans. Globally, the reported cases of seasonal influenza viruses (SIVs) rise up to 3–5 million during epidemics with an estimated death toll of 290,000–650,000 per year [1]. The Global Influenza Surveillance and Response System (GISRS), a surveillance system of the World Health Organization (WHO), analyses the incidences of avian and zoonotic influenza virus to accurately estimate the severity of the disease. As of March 5–18, 2018, GISRS-WHO has reported 46.8% cases of influenza A virus (where 64% were influenza A(H1N1)pdm09 cases and 36% were infected with H3N2) and 53.2% of influenza B virus (where 91% were B-Yamagata strain and 9% were B-Victoria) [2]. The co-morbidity condition (such as diabetes, heart or liver disease) or the immuno-compromised condition of patients is the predominant cause of mortality associated with influenza virus.

Influenza virus belongs to the *Orthomyxoviridae* family and is categorized as influenza A virus (IAV), influenza B virus (IBV), and influenza C virus (ICV). The genome of influenza virus is segmented with 8 negative-sense single-stranded viral RNA (vRNA) strands which code for 11 proteins in cases of IAV and IAB, whereas IAC has seven vRNA segments that code for nine proteins. These segments are named after their main proteins such as segment 1-PB2 (polymerase basic 2), segment 2-PB1 (polymerase basic 1), segment 3-PA (polymerase acid), segment 4-HA (hemagglutinin), segment 5-NP (nucleoprotein), segment 6-NA (neuraminidase), segment 7-M (matrix), and segment 8-NS (non-structural) [3]. Influenza vRNA has heterotrimeric RNA-dependent RNA polymerase (RdRp) at the 5′ and 3′ end of the segment

and the internal part of vRNA is bound with several nucleoproteins (NP) forming viral ribonucleoprotein complexes (vRNP) [4]. Hemagglutinin (HA) and neuraminidase (NA) are envelope glycoproteins responsible for the antigenic variation and the generation of different strains of influenza virus. HAs are of 16 subtypes (H1–H16) and NA has nine subtypes (N1-N9) [5]. As a result of the antigenic drift, SIVs are generated due to several point mutations in the *HA* and *NA* genes caused by RdRp [6]. Thus, the antibodies generated during primary infection with the influenza virus are unable to neutralize the drifted strains of SIVs, leading to epidemics or pandemics. Considerable numbers of individuals are always at risk of getting infected with influenza viruses, thus creating a state of alertness. In addition to SIVs, there are several pandemic viruses generated due to the antigenic shift, where the newly drifted strains of viruses have the ability to cross species barriers, as a result of the re-assortment of a viral genome with other influenza viruses (human or non-human).

2. Transmission

The natural reservoirs of IAV are duck and waterfowl allowing direct virus transmission to other avian hosts as well as in others via crossing species barrier such as in humans,

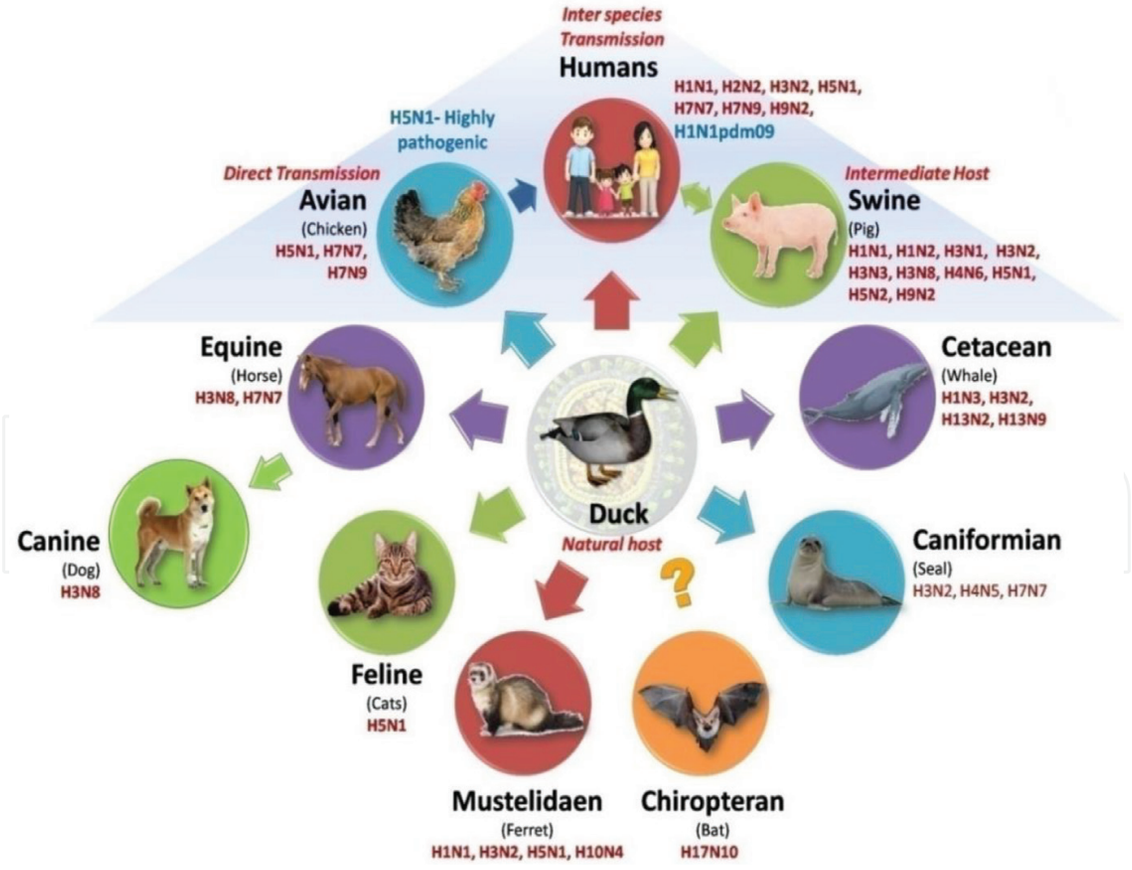

Figure 1. Transmission cycle of IAV: The triangle in the figure describes the most important transmission cycle of IAV, where the virus is directly transmitted from the natural host, duck to avian, and further transmitted to the human, or the virus is transmitted from duck to human by inter-species transmission or via pig where pig acts as an intermediate host between the duck and the human. The other low pathogenic hosts of IAV are cat, horse, dog, ferret, seal, and whale. The subtypes of IAVs responsible for causing influenza in their host are also mentioned.

cats, pigs, horses, ferrets, seals, and whales (**Figure 1**). Avian IAV such as H5N1 and H9N2 are known to cause bird flu, whereas H1N1 and H3N2 are responsible for swine flu. IAVs are also categorized as seasonal and pandemic based on genetic variation and the severity of influenza disease; IAV transmission occurs by direct or indirect contact, inhaling virus-infected droplets or small droplet nuclei, being exposed to diseased poultry, feeding raw or undercooked poultry, transplacental transmission, or drinking water contaminated by viruses [7]. The serological evidence validated that human-to-human transmission of influenza viruses is inefficient; however, in some rare cases human-to-human transmission was observed during an outbreak of the highly pathogenic avian influenza viruses (HPAI) of H5N1 [8]. Influenza virus enters the human body through the respiratory tract and its incubation period is 1–7 days. The common symptoms associated with influenza are respiratory distress, fever, headache, cold, abdominal pain and joint pain [9]. With the progression of the disease, other symptoms observed are bloody sputum and pneumonia that further cause respiratory failure leading to acute respiratory distress syndrome (ARDS) [10]. IAV-infected patients can be diagnosed by reverse transcription-polymerase chain reaction (RT-PCR), viral culture, and the high levels of HA antigen- specific neutralizing antibodies.

3. Life cycle of influenza A virus

The IAV enters in the host cell by binding with surface receptors possessing sialic acid moiety. Viruses are internalized by endocytosis and the uncoating of the virus by matrix protein 2, an ion channel. The vRNA is released in the cytoplasm and is imported to the nucleus where vRNA is transcribed and replicated by using its polymerase [11]. Thus, these steps lead to the synthesis of a positive sense complementary RNA (cRNA) and viral messenger RNA (vmRNA) with 5′cap and 3′ poly (A) tail. The influenza virus polymerase does not exhibit capping activity at the 5′end; hence, they have to depend on host-capped mRNAs where they capture its 5′cap, a process known as cap snatching [12]. The viral m-RNA is translated in the cytoplasm after being exported from the nucleus and viral proteins, and nucleoproteins are synthesized by cellular ribosomes. Translated viral proteins re-enter the nucleus and bind to the vRNAs to generate viral ribonucleoproteins (vRNPs). Following nuclear export, progeny vRNPs and viral proteins are assembled to form virions which later egress from the host cell.

4. Pandemics and outbreaks of human influenza A virus

The prominent IAVs causing pandemics and outbreaks in various parts of the world are shown in the **Figures 2** and **3**, respectively. The 1918 spread of human influenza A(H1N1) virus has caused death of approximately 40–50 million people worldwide. This virus had again emerged in 2009 and caused a death toll of 4100 people. The clinical presentations were similar to the earlier strain that led to a less severe response. The twenty-first-century influenza viruses that cause infections in humans are briefly discussed below.

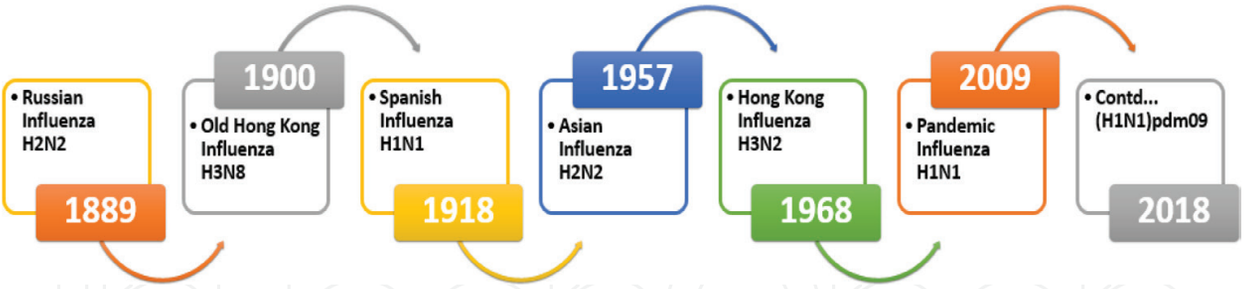

Figure 2. The pandemics of influenza A viruses. Noted influenza A virus pandemics are shown in the figure till 2018.

4.1. Influenza A(H5N1) virus

The first outbreak of human infection due to influenza A(H5N1) virus occurred in Hong Kong in 1997 with 18 cases and 6 deaths, following its re-emergence in regions of Southeast Asia during 2003, where 392 individuals were infected and 247 fatal outcomes were reported [13].

2018- Continued	• (H1N1)pdm09, H3N2
2017-2018	• (H1N1)pdm09, H3N2, H5N1, H5N2, H7N7, H5N6, H5N8, H7N8, H7N9, H7N3
2016-2017	• (H1N1)pdm09, H3N2, H5N1, H5N2, H7N7, H5N6, H5N8, H7N8
2015-2016	• (H1N1)pdm09, H3N2, H5N1, H5N2, H7N7, H5N6, H5N8
2014-2015	• (H1N1)pdm09, H3N2, H5N1, H5N2, H7N7, H7N2, H5N6
2013-2014	• (H1N1)pdm09, H3N2, H5N1, H5N2, H7N7, H7N2
2012-2013	• (H1N1)pdm09, H3N2, H5N1, H5N2, H7N7
2011-2012	• (H1N1)pdm09, H3N2, H5N1
2010-2011	• (H1N1)pdm09, H3N2, H5N1
2009-2010	• (H1N1)pdm09, H5N1
2008-2009	• H1N1, H3N2, H5N1, H7N7
2007-2008	• H1N1, H3N2, H5N1
2006-2007	• H1N1, H3N2, H5N1
2005-2006	• H1N1, H3N2, H5N1, H5N2
2004-2005	• H1N1, H3N2, H5N1, H5N2
2003-2004	• H1N1, H3N2, H5N1
2002-2003	• H1N1, H3N2, H1N2
2001-2002	• H1N1, H3N2
2000-2001	• H1N1

Figure 3. Recent outbreaks of influenza A virus in humans. The prominent influenza A viruses of twenty-first century causing most number of cases are shown in the picture.

This HPAI H5N1 virus further infected humans as well as migratory birds. The reported mortality rate was ~60% of the infected human population [14] and ~6000 deaths of migratory birds have been reported in Western China [15, 16].

4.2. Influenza A(H1N1)pdm09 virus

The first human infection from pandemic influenza A(H1N1)2009 virus was reported in Mexico and the United States in March 2009, and later it was transmitted globally [17]. The number of cases reported worldwide to the WHO in the period from March to September 2009 was 340,000 with 4100 deaths. In India, influenza A(H1N1)2009 was the pandemic, with 10,036 laboratory-reported cases and 308 deaths. The susceptible age groups infected were children of age less than 5 years and adults of more than 65 years, while pregnant women were at high risk of infection [18].

4.3. Influenza A(H7N9) virus

A highly pathogenic novel strain of IAV is H7N9, first reported in China in 2013. The Chinese Center for Disease Control and Prevention (China CDC) has actively investigated the first 82 patients infected with influenza A(H7N9) in the provinces of China [19] where the number of reported cases was 131 with 32 deaths. Based on the weekly report on April 20, 2017, the WHO has identified 1393 laboratory-observed cases of H7N9 virus with 534 deaths. Further, the WHO has assessed that within 2 months of the H7N9 outbreak, the number of cases were as many as of H5N1 in 10 years and till date cases of H7N9 are reported [20].

5. Immunobiology

Influenza viruses enter in humans through the respiratory tract by the oral or nasal route and the first barrier for the virus is to cross the mucous layer surrounding the respiratory epithelium. Then, through the mucous layer, influenza virus has to attach and internalize these epithelial cells to cause infection. The host defense mechanism is activated to prohibit the spread of the virus. Thus, the pattern recognition receptors (PRRs) detect the pathogen-associated molecular patterns (PAMPs) of the infectious viral agents and activate the host's innate immune system by the secretion of type-I interferons, pro-inflammatory cytokines and chemokines [21]. Respiratory tract cells such as macrophages, dendritic cells (DCs), pneumocytes and plasmacytoid DCs (pDCs) actively participate in production of type-I interferons that stimulates a pool of genes called interferon-stimulated genes (ISGs) (mentioned in **Table 1**) which enhance the antiviral activity of host defense system [22, 23]. These PRRs include the toll-like receptors such as TLR3 that recognizes the viral dsRNA present in infected cells; TLR7 and TLR8 detect viral ssRNA present in endosomes of infected cells; retinoic acid-inducible gene I (RIG-I) recognizes the virus present in the cytosol of infected cells [24]. The human respiratory epithelial cells constitutively express TLR3 that induces the generation of pro-inflammatory cytokines on the detection of influenza virus that stimulates the infiltration of leukocytes and CD8+ T cells restricting virus replication [25]. These

Interferon-stimulated genes (ISGs)	Intracellular location	Mode of action
Cholesterol 25-hydroxylase ($CH_{25}H$)	Cytosol	Inhibits fusion of virus with host cell membrane
2'-5'-Oligoadenylate synthase (OAS) and RNase L	Cytosol	Stimulates cleavage of viral RNA
Protein kinase R (PKR)	Cytosol	Inhibits translation and activates downstream NF-κB pathway
ISG15	Cytosol	Ubiquitin-like protein that targets newly translated viral proteins for modification
Tripartite motif-containing protein 22 (TRIM22)	Nucleus	Binds with nucleocapsid for proteasomal degradation
MX1	Nucleus	Inhibits viral transcription in nucleus
IFITM3 and other IFN-inducible transmembrane (IFITM) proteins	Endosomes	Inhibits viral attachment, fusion and endocytosis
Viperin	Lipid droplets and the cytosolic face of the endoplasmic reticulum	Inhibits egression of virus by blocking formation of the lipid raft

Table 1. Role of pertinent interferon-stimulated genes (ISG) in controlling influenza virus infection (adapted from Ref. [4]).

pro-inflammatory cytokines cause local inflammation and fever that activate the adaptive immune response against influenza virus. Chemokines instruct downstream immune cells by recruiting neutrophils, monocytes and natural killer (NK) cells to the respiratory tract. NK cells target and eliminate the virus-infected epithelial cells initiating viral clearance [26]. Monocytes and neutrophils participate in the removal of dead cells infected with virus. Alveolar macrophages cause the phagocytic clearance of infected cells, a crucial step for virus clearance [27]. The innate and adaptive immune system works hand in hand for the clearance of the influenza virus from the host system.

6. Antiviral therapeutics

Numerous antiviral drugs inhibiting influenza viruses are available. The most targeted sites for restricting influenza viruses are matrix protein 2 and NA, inhibited by antivirals such as adamantanes (amantadine and rimantadine), oseltamivir, and zanamivir [28]. The adamantanes interfere with viral uncoating and had shown toxic effects that lead to the generation of adamantanes-resistant strains of the influenza virus. Furthermore, the budding off progeny virions from host cells is impeded by the neuraminidase inhibitors that caused only one round of replication, hence preventing the spread of infection. Influenza viruses such as influenza A(H3N2) and A(H1N1)pdm09 were observed to be resistant for adamantanes; therefore, for the clinical treatment of influenza virus A, adamantanes are not recommended. However, IAV and influenza B virus are susceptible to oseltamivir and zanamivir [29]. The other potential targeted sites are viral entry, HA, pH-dependent endosomal fusion, nucleoproteins and polymerase proteins of influenza viruses. HA1 and HA2 play key roles in the invasion of the influenza virus in target host cells. HA1 binds with the sialic acid receptors while HA2

contributes in the fusion and internalization by endocytosis. Furthermore, a novel antiviral N-stearoyllipopeptide of C18-ARLPR inhibits the viral replication of influenza A/Puerto Rico/8/34 (H1N1) and A/Aichi/2/68 (H3N2) effectively with low toxicity [30]. This peptide adequately binds to the sialic acid-binding site of HA1 subunit due to its structural similarity.

7. Complementary and alternative medicine (CAM)

The National Centre for Complementary and Integrative Health-National Institute of Health (NCCIH-NIH), the United States, describes complementary and alternative medicine (CAM) as a collection of varied medicinal practices, natural products, and health-care systems, different from conventional medicine [31]. CAMs treat the disease effectively with fewer side effects and low toxicity [32]. Several plant products are globally applied for the treatment of influenza, though the mechanism of their action is still unknown. The extracts of plants are prepared at very high dilution and are given in small doses. The interaction of active components of plant extracts and viral proteins of the influenza virus is further explored for discovering a potent organic antiviral against a pandemic virus such as H1N1. Some of the reported natural compounds for the treatment of human influenza are baicalin, tinosporon, allicin, curcumin, ursolic acid, carvacrol, ajoene, methanol, andrographolide, coumarin, theaflavin, and eugenol [33]. In *in silico* study, these natural compounds blocked H1N1 NA effectively with significant values of binding energies. Several traditional plants such as *Trachyspermum ammi*, *Ocimum sanctum*, *Zingiber officinalis, Allium sativum, Curcuma longa*, *Tinospora cordifolia,* and *Mentha piperita* are potential antiviral agents against H1N1 swine flu. Another plant-based antiviral agent, ginseng (*Panax quinquefolium*), has triterpenes and saponins that are the potent inhibitors of influenza A(H1N1) pdm09 [34]. The CAM therapies for the treatment of influenza virus also include influenzinum that induces cytokine release from macrophages and furthermore activates the innate immune response [3]. In a study, IAV H3N2-infected MDCK cells were treated with influenzinum and it was observed that there was no cytotoxic effect due to influenzinum, yet the morphology of cells were altered [35].

8. Prevention and control

The transmission of influenza virus between humans and other hosts like avian and swine was reported to be possible and significantly caused pandemics in various countries [36]. The viruses responsible for infecting humans are HPAI or low-pathogenicity avian influenza (LPAI) viruses. Owing to the enormous ability of re-assortment (due to shift and drift) in influenza viruses, absolute prediction of the responsible subtype(s) for the next pandemic infection is impractical. Thus, a vaccine which can effectively target a broad range of influenza viruses is required for the protection of the human host. The development of the vaccine should be dependent on several strategies such as epidemiological data of the previous pandemic influenza viruses, the presence of viruses in nature, and viruses responsible for infecting human population. The current influenza vaccines are live-attenuated influenza vaccines (LAIV), influenza-inactivated vaccine (IIV), recombinant subunit, DNA and vectored virus vaccine [37]. According to Centers for Disease Control and

Prevention (CDCs), the United States, available vaccines are of two types—trivalent and quadrivalent flu vaccines. Trivalent influenza vaccine protects against influenza A(H1N1) and A(H3N2) as well as influenza B virus. The standard-dose trivalent flu shots are IIV 3, given to individuals between 18 and 64 years. The CDC has not recommended using LAIV as the vaccines for the year 2017–2018 due to its low effectiveness found during 2013–2017. There are some limitations associated with influenza virus vaccines suggesting that the circulating virus and the vaccine virus should be of same strains to give a high efficacy or else the vaccine might provide a false sense of security. The early influenza vaccination of individuals at a high risk might prevent influenza from becoming a pandemic. The Advisory Committee on Immunization Practices (ACIP) has recommended to primarily providing vaccination to children, pregnant women, individuals of age more than 65 years, and to people suffering from chronic ailments [38]. The other effective methods to control influenza are properly washing hands, use of masks, and covering mouth during coughing and sneezing, avoiding physical contacts with influenza-infected individuals, wearing gloves while working with infected poultry or swine, and the intake of effective antiviral medications.

9. Conclusions and future perspectives

Several factors play a pivotal role in preventing influenza virus infection such as increasing antigenic and genetic variants of influenza virus subtypes, the ability to cross the species barrier, antiviral drug resistance, incapability in predicting the upcoming pandemic virus, the low probability of correctly matching the circulating and vaccine viruses, and the high cost of vaccination. Thus, a robust surveillance system that monitors the human influenza viruses will provide the candidate virus vaccine (CVV) as an adequate strategy required for preparing the pandemics. Apart from this, a comprehensive understanding at the molecular and genetic level of the avian and swine influenza virus will strengthen us in understanding their mechanism of re-assortment and transmission in humans. The veterinary vaccines designed for avian and swine population should be examined to evaluate their efficacy on the avian and swine influenza viruses. Furthermore, there is a crucial requirement of the universal vaccine that can target both seasonal and pandemic influenza viruses. Awareness regarding the prevention and control methods of influenza should be widely spread.

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