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Research Article

Review on Influenza A virus

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Abstract

Influenza A virus is caused by Orthomyxoviridae family and can be divided into highly pathogenic avian influenza virus and low pathogenic avian influenza virus based on the severity of the disease they cause. Potential modes of transmission of influenza virus include direct contact with infected individuals, exposure to virus-contaminated objects (fomites), and inhalation of infectious aerosols. Influenza replicates in epithelial cells throughout the respiratory tree (both upper and lower respiratory tract). Influenza A virus infection could result in mild to severe signs and symptoms in human. Husbandry practices, age, species of poultry and pathogenicity of the influenza virus strain are some of the factors that determine clinical sign in poultry. Specific Antibody Negative eggs (SAN) or Specific pathogen free embryonated chicken eggs inoculation are the preferred method for growing influenza A viruses. The influenza A virus genomes comprises eight negative-sense, single-stranded viral RNA segments. Treatment could be Symptomatic or direct treatment of influenza the virus. According to Center for Disease Control both trivalent (three-component) and quadrivalent (four-component) flu vaccine are recommended.

Keywords: Influenza A virus; Orthomyxoviridae; Influenza types A, B, C and D

Introduction

Influenza is an infectious disease with symptoms of the common cold such as chills, high fever, sore throat, muscle pains, severe headache, coughing, bleeding from nose, weakness and general discomfort, but it is a much more severe disease as it can lead to life-threatening complications (like pneumonia) and death. Influenza is caused by four types of RNA viruses called influenza types A, B, C and D, which all belong to the Orthomyxoviridae family. The so called "flu" in humans is generally caused by the viruses A and B, which are transmitted by aerosols from infected individuals or through contact with infected animals. Natural hosts for most influenza A viruses are wild aquatic birds such as shorebirds, swans, wild ducks and geese [1,2].

Based on severity of the disease they cause, influenza A viruses are divided into two groups. The severe form of Avian Influenza (AI) termed Highly Pathogenic (HPAI), at one time known as 'fowl plague', is one of the most feared diseases of poultry and other birds. The very virulent viruses causing HPAI have been restricted to subtypes H5 and H7, although not all viruses of these subtypes cause HPAI. All other viruses cause a much milder disease consisting primarily of mild respiratory disease, depression and egg production problems in laying birds; these are termed Low Pathogenic AI (LPAI) viruses [3].

Influenza A viruses are divided into subtypes on the basis of two proteins on the surface of the virus: Hemagglutinin (HA) and Neuraminidase (NA). Currently there are 18 HA and 11 NA subtypes. It is possible for any of these HA and NA protein to combine and result in new virus. HA acts to attach the virus into host cells and subsequently fuse it to cell membranes, which is essential for the virus life cycle. The major function of viral Neuraminidase (NA) is at the final stage of infection when NA cleaves sialic acid from cell surface and progeny virions facilitating virus release from infected cells [2,4,5].

Influenza A viruses are responsible for causing pandemics in humans. During the twentieth century, three pandemics by influenza A viruses occurred in humans. In 1918, the wholly avian influenza A virus, H1N1, infected humans, resulting in over 50 million deaths [6]. The H2N2 and H3N2 viruses, which were responsible for claiming thousands of human deaths during the pandemics in 1957 and 1968, respectively, resulted from a re-assortment between genes from humans and avian influenza viruses [7,8]. In the twenty first century, a pandemic outbreak of swine origin H1N1 influenza virus, containing gene segments from swine and avian influenza viruses, occurred in humans in 2009 [9]. Lack of specific clinical signs and antigenic variation among different influenza A viruses are the challenges to diagnose avian influenza virus infection. Isolation, identification and characterization of the virus are the conventional laboratory techniques used to diagnose the virus [10].

The best way to prevent infection with avian influenza A viruses is to avoid sources of exposure whenever possible. Infected birds shed avian influenza virus in their saliva, mucous and feces. People who work with poultry or who respond to avian influenza outbreaks are advised to follow recommended bio security and infection control practices; these include use of appropriate personal protective equipment and careful attention to hand hygiene. Analyses of available avian influenza viruses circulating worldwide suggest that most viruses are susceptible to oseltamivir, peramivir, and zanamivir. However, some evidence of antiviral resistance has been reported in HPAI Asian lineage avian influenza A (H5N1) viruses ("Asian H5N1 viruses") and Asian lineage avian influenza A (H7N9) viruses ("Asian H7N9 viruses"). Monitoring for antiviral resistance among avian influenza A viruses is crucial [2]. Objective of this paper is to review general feature of Avian influenza A virus.

Avian Influenza A Virus

Etiology

Influenza is caused by four types of RNA viruses called influenza types A, B, C and D, which all belong to the Orthomyxoviridae family

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[1,2]. Influenza viruses have segmented, negative sense, single strand RNA genomes [11]. Influenza A viruses infecting poultry can be divided into Highly Pathogenic Avian Influenza Virus (HPAI) and Low Pathogenic Avian Influenza Virus LPAI) based on the severity of the disease they cause [3]. Influenza A viruses are divided into subtypes on the basis of two proteins on the surface of the virus: Hemagglutinin (HA) and Neuraminidase (NA). There are 18 known HA subtypes and 11 known NA subtypes. Many different combinations of HA and NA proteins are possible [2].

Host and transmission

Influenza virus has been isolated from aquatic birds, poultry, humans, pigs, horses, seals, dogs and mink [12]. Infection and transmission of avian influenza viruses among nonhuman mammals, particularly swine, facilitate their subsequent transfer to humans [13].

Influenza replicates in epithelial cells throughout the respiratory tree (both upper and lower respiratory tract) [14]. Potential modes of transmission of influenza virus include direct contact with infected individuals, exposure to virus-contaminated objects (fomites), and inhalation of infectious aerosols (Figure 1) [15]. The influenza virus life cycle is initiated by the binding of viral HA to receptors on host cells. After endocytosis and HA-mediated fusion of the viral and cellular membranes, viral ribonucleoprotein complexes are released into the cytoplasm, transported to the nucleus, and replicated and transcribed by the viral polymerase complex. Newly formed viral ribonucleoprotein complexes and structural proteins are transported to the plasma membrane, where the new viruses are formed and bud [16].Viral HA protein is the major host restriction factor that limits interspecies transmission and the establishment of virus lineages in new hosts. Influenza viruses bind to sialyloligosaccharides on glycoproteins or glycolipids on the surface of host cells to infect them. Sialic acids can be linked to the penultimate galactose through different linkages, such as an α2, 3 or an α2, 6 linkage (Siaα2, 3Gal or Siaα2, 6Gal). Influenza A viruses circulating in wild water fowl efficiently bind to Siaα2, 3Gal sialic acid [17,18]. Influenza viruses circulating in humans adapted to bind efficiently to Siaα2, 6Gal [19]. The epithelial cells of the pig trachea contain bothSiaα2, 3 Gal andSiaα2, 6Gal [20-22], which may explain why pigs can be infected efficiently by human and avian influenza viruses; consequently, pigs may serve as 'mixing vessels' for the reassortment of avian, swine, and human influenza viruses.

The NA protein encodes a sialidase that cleaves sialic acids from sialyloligosaccharides; this enzymatic activity is vital for efficient infection and release of viruses from host cells, as the virus would otherwise be trapped by sialic acids on mucus or remain attached to the sialic acids on the host cells, resulting in large viral aggregates. HA mediated binding to, and NA-mediated release from sialicacids therefore must be balanced for efficient virus replication. The NA proteins of all influenza viruses exhibit significantly higher enzymatic activity against Siaα2, 3 Gal than against Siaα2, 6 Gal [23-25].

Influenza viral replication and transcription are catalyzed by the viral polymerase complex, composed of the PB2, PB1, and PA proteins. Although all three polymerase subunits affect influenza virulence, PB2 is the main polymerase determinant for influenza virulence and host range and thus, for influenza virus adaptation to new hosts [26-28].

Clinical signs

The reported signs and symptoms of avian influenza A virus infections in humans have ranged from mild to severe and included conjunctivitis, influenza-like illness (e.g., fever, cough, sore throat, muscle aches) sometimes accompanied by nausea, abdominal pain, diarrhea, and vomiting, severe respiratory illness (e.g., shortness of breath, difficulty breathing, pneumonia, acute respiratory distress, viral pneumonia, respiratory failure), neurologic changes (altered mental status, seizures), and the involvement of other organ systems (Figure 2). Asian lineage H7N9 and HPAI Asian lineage H5N1 viruses have been responsible for most human illness worldwide to date, including most serious illnesses and highest mortality [2].

Husbandry practices, age, species of poultry and pathogenicity of the influenza virus strain are some of the factors that determine clinical sign in poultry. Clinical signs may include: ruffled feathers, soft-shelled eggs, depression and droopiness, sudden drop in egg production, loss of appetite, cyanosis (purplish-blue coloring) of wattles and comb, edema and swelling of head, eyelids, comb, wattles, and hocks, diarrhea, blood-tinged discharge from nostrils, in coordination, including loss of ability to walk and stand, pin-point hemorrhages (most easily seen on the feet and shanks), respiratory distress, increased death losses in a flock [29].

Incubation period

The incubation period in poultry can be a few hours to a few days in individual birds, and up to 2 weeks in the flock. In mammals incubation period of the virus could be as short as1 to 2 days [30].

Isolation and characterization of Avian influenza A virus

Sample collection: Oropharyngeal swabs, cloacal swabs and intestinal contents need to be included during sample collection from dead birds. Lung, trachea, spleen, kidney, air sacs, brain, heart and

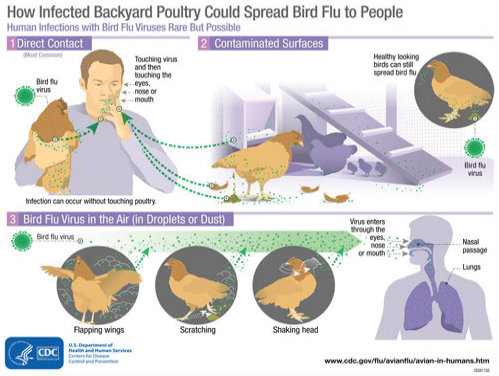

Figure 1: How infected backyard poultry could spread Bird flu to people.

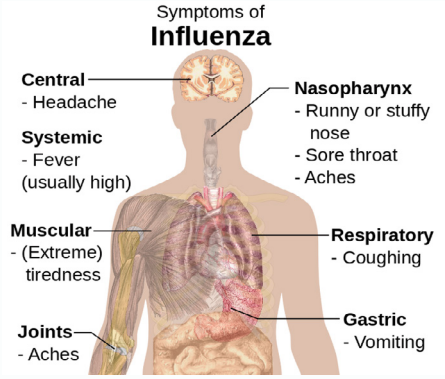

Figure 2: Symptoms of influenza virus in human.

liver samples which could be processed as a pool or separately should also be included. Cloacal swabs and oropharyngeal swabs are required to be collected from live birds [31].

Isotonic Phosphate-Buffered Saline (PBS), pH 7.0-7.4 with antibiotics or a solution containing protein and antibiotics should be used to place the sample. Minced tissues and faeces need to be prepared as 20% (w/v) suspensions in the antibiotic solution. Immediate processing of the sample is preferred (1 to 2 hour's incubation at room temperature). Samples could be stored at -80°C for long period [32].

Virus propagation: Specific Antibody Negative eggs (SAN) or Specific pathogen free embryonated chicken eggs inoculation are the preferred method for growing influenza A viruses. Allantoic sac of three to five embryonated SPF or SAN chicken eggs incubated for 9-11 days are used to inoculate supernatant fluids of faeces or tissue suspensions obtained through clarification by centrifugation at 1000 g. The eggs are incubated at 37°C (range 35°C - 39°C) for 2-7 days. Eggs containing dead or dying embryos as they arise, and all eggs remaining at the end of the incubation period, should first be chilled to 4°C for 4 hours or overnight, and the allantoic fluids should then be recovered and tested with a screening test (such as haemagglutination [HA] test), influenza A type-specific test (such as Agar Gel Immunodiffusion Test (AGID) or Solid-Phase Antigen-Capture Enzyme-Linked Immunosorbent Assays (ELISA) or influenza A subtype-specific test (such as Haemagglutination Inhibition (HI) and Neuraminidase Inhibition (NI) tests) or a molecular test to detect influenza A specific nucleic acid signatures (such as Real-Time Reverse Transcription Polymerase Chain Reaction (RT-PCR) test) [32].

Influenza A virus genome structure and proteins: Influenza viruses are roughly spherical, although somewhat pleomorphic, particles, ranging from 80 nm to 120 nm in diameter [33,34]. A characteristic feature of influenza virus particles is their external layer of approximately 500 spike-like projections. These spikes represent the envelope glycoproteins HA (which has a rod-like shape) and NA (which is mushroom shaped) [34] (Figure 3).

The influenza A virus genomes comprises eight negative-sense, single-stranded Viral RNA (vRNA) segments. Each segment is associated with multiple copies of nucleoprotein and with the viral transcriptase consisting of RNA polymerase components PB1, PB2 and PA, thus forming the RNP complex. RNA segments 1-6 of influenza A viruses encode a single protein each. Segment 7 encodes two proteins, M1 and M2, with overlapping reading frames. Segment 8 encodes the non-structural proteins NS1 and NS2, with superimposed reading frames (Table 1) [33].

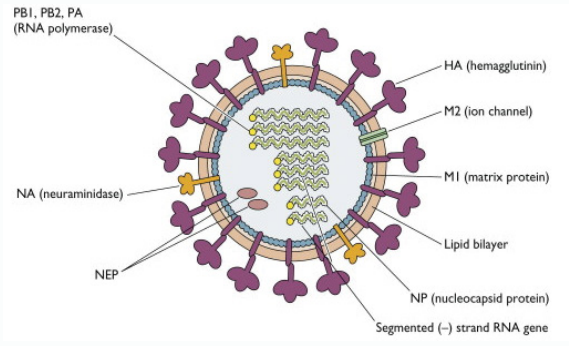

Figure 3: Influenza virus structure.

Influenza A Virus Testing Methods: Influenza virus can be tested by one of the following techniques (Table 2) source: (https://www.cdc.gov/flu/professionals/diagnosis/table-testing-methods.htm)

Treatment

Treatments for influenza include a range of medications and therapies that are used in response to disease influenza. Treatment could be Symptomatic or direct treatment of influenza the virus. Nneuraminidase inhibitors, such as zanamivir and oseltamivir, or inhibitors of the viral (matrix2) M2 protein, such as amantadine and rimantadine are the two main classes of antiviral drugs used to treat influenza Virus. The sooner these drugs are taken after infection the better they can reduce the severity of the disease. However, virus strains have emerged that show drug resistance to both classes of drug [35].

Table 1: Influenza A virus RNA segments and the proteins they encode. Influenza A viruses have eight gene segments encoding 10 different proteins, segments 7 and 8 encoding two proteins each (Lamb and Krug, 2001).

RNA segments (number of nucleotides)	Gene product (number of amino acids)	Molecules per virion
1 (2341)	Polymerase PB2 (759)	30-60
2 (2341)	Polymerase PB1 (757)	30-60
3 (2233)	Polymerase PA (716)	30-60
4 (1778)	Haemagglutinin (566)	500
5 (1565)	Nucleoprotein (498)	1000
6 (1413)	Neuraminidase (454)	100
7 (1027)	Matrix protein M1 (252)	3000
	Matrix protein M2 (97)	20-60
8 (890)	Non-structural proteins	
	NS1 (230)	-
	NS2 (121)	130-200

Conclusion

Influenza is caused by four types of RNA viruses called influenza types A, B, C and D, which all belong to the Orthomyxoviridae family. Influenza A viruses are divided into subtypes on the basis of two proteins on the surface of the virus: Hemagglutinin (HA) and Neuraminidase (NA). There are 18 known HA subtypes and 11 known NA subtypes. Many different combinations of HA and NA proteins are possible. The influenza virus life cycle is initiated by the binding of viral HA to receptors on host cells. The preferred method of growing influenza A viruses is by the inoculation of Specific Pathogen Free (SPF) embryonated chicken eggs, or Specific Antibody Negative (SAN) eggs. For vaccination both trivalent (three-component) and quadrivalent (four-component) flu vaccine can be used. Treatments for influenza include a range of medications and therapies that are used in response to disease influenza.

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Table 2: Influenza A virus diagnostic techniques.

Method[1]	Acceptable Specimens	Test Time
Rapid Influenza Diagnostic Tests[2] (antigen detection)	Nasopharyngeal swab, aspirate or wash, nasal swab, aspirate or wash, throat swab	<15 min.
Rapid Molecular Assay (influenza viral RNA or nucleic acid detection)	Nasopharyngeal swab, nasal swab	<20 minutes[3]
Immunofluorescence, Direct (DFA) or Indirect (IFA) Florescent Antibody Staining (antigen detection)	Nasopharyngeal swab or wash, bronchial wash, nasal or endotracheal aspirate	1-4 hours
RT-PCR[3] (singleplex and multiplex; real-time and other RNA-based) and other molecular assays (influenza viral RNA or nucleic acid detection)	Nasopharyngeal swab, throat swab, NP[5] or bronchial wash, nasal or endotracheal aspirate, sputum	Varies (1 to 8 hours, varies by the assay)
Rapid cell culture (shell vials; cell mixtures; yields live virus)	Nasopharyngeal swab, throat swab, Nasopharyngeal or bronchial wash, nasal or endotracheal aspirate, sputum; (specimens placed in Viral transport media)	1-3 days
Viral tissue cell culture (conventional; yields live virus)	Nasopharyngeal swab, throat swab, Nasopharyngeal or bronchial wash, nasal or endotracheal aspirate, sputum (specimens placed in Viral transport media)	3-10 days

Where; 1=Serologic (antibody detection) testing. Serological testing for detection of antibodies to seasonal influenza viruses is useful for research studies and requires collection of appropriately timed acute and convalescent serum specimens and testing of paired sera at specialized research or public health laboratories 2=Chromatographic- and/or fluorescence-based lateral flow and membrane-based immunoassays. Some approved rapid influenza diagnostic assays utilize an analyzer reader device; 3=Reverse transcription polymerase chain reaction, including FDA-approved test systems, reference laboratory testing using ASR or lab-developed reagents. Some approved molecular assays can produce results in approximately 60-80 minutes. (https://www.cdc.gov/flu/professionals/diagnosis/table-testing-methods.htm).

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