**SECTION 5. VIRUSES**

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## 5.1 Influenza virus infection in human: epidemiology; genetics; patogenesis; prophylactics

Influenza virus infections is one of the most common uncontrolled infections that are registered on all continents. Influenza is a major global health problem affecting all countries, with approximately one billion cases of seasonal influenza occurring worldwide each year, causing three to five million severe cases, including up to 650,000 respiratory-related deaths with the flu In addition, new influenza viruses are constantly appearing - they can cause pandemics, which, despite the level of development of modern medicine, can lead to large-scale social disorders and millions of deaths. The peculiarity of the infection is the speed of its spread. Influenza viruses cause annually recurrent respiratory disease in humans with significant impact on human health as well as on economy. In recent years, new properties of the influenza virus have been discovered: the ability to exchange genetic information with animal and bird influenza pathogens; the influenza virus can remain in the human body for a long time after recovery. Although influenza B viruses are almost exclusively found in humans, influenza A viruses (IAVs) circulate in the human population as an annually recurring epidemic disease, and emerge from a huge zoonotic reservoir. Characterized by their ability to rapidly acquire adaptive mutations in a process called antigenic drift, IAV gradually evade the human immune response [348].

Two different genera of the virus family Orthomyxoviridae, influenza A and B, can cause a contagious respiratory disease in humans. Virions have a spherical shape with a diameter of 80-120 nm, less often rod-like and thread-like; consist of a core and an outer lipoprotein shell. The core contains a single-stranded linear fragmented minus-strand RNA, a protein capsid surrounded by an additional membrane - a layer of matrix protein.

The nucleocapsid has a helical type of symmetry. On the surface of the supercapsid shell there are spikes of glycoprotein nature, some of which are

hemagglutinin (HA), others are neuraminidase (NA). Internal structural proteins: nucleocapsid protein (NP) - the main internal protein, three polymerase proteins (PA, PB1, PB2) and matrix protein (M1). Proteins M2 (ion channel), NS1, NS2 are synthesized during virus reproduction. Hemagglutinin (HA) is the main strain-specific antigen of the virus with a high degree of uncontrolled variability. It is the most immunogenic protein that causes the formation of protective antibodies. HA - antigen that causes: formation of virus-neutralizing antibodies; provides adsorption of the virus on cells, in particular human erythrocytes, as a result of which their gluing occurs – hemagglutination.

Neuraminidase (NA) is a virus enzyme that takes part in the entry of the virus into human cells; accelerates the exit of the virus from the cell, preventing the aggregation of viral particles. NA has antigenic properties. Antibodies formed against NA have projective (virus-neutralizing) properties, but do not neutralize the infectious activity of the virus to the same extent as NA.

Hemagglutinin and neuraminidase are factors of influenza virus aggression. Both surface antigens are very variable, which is the reason for the appearance of new antigenic variants of the virus. Influenza A viruses are present in a large number of mammalian species, poultry, and particularly wild birds, with currently 18 or 11 variants known for HA or NA, respectively, where the recently discovered bat-isolates H17/18 and N10/11 seem to be quite distinct from avian and mammalian strains [349].

The genome of the influenza virus is a single-stranded, fragmented "minus" RNA, which closely associated with capsid proteins to form 8 ribonucleoproteins (RNPs) of helical symmetry. Each fragment of RNP is associated with a viral RNA-dependent RNA polymerase.

A characteristic feature of influenza viruses is the variability of HA and NA antigens. The variability of the surface antigens of the influenza virus is related to the fragmentary structure of RNA and occurs in the form of drift and shift. Antigenic drift is minor changes in the NA gene, which are caused by point mutations that lead to minor changes in surface blood pressure. Antigenic shift is a complete replacement of

a gene, which leads to qualitative changes in the subtype of hemagglutinin and neuraminidase and the appearance of fundamentally new antigenic variants of the virus

Genetic shuffling, or reassortment (genetic recombination) is a process that occurs when two strains of influenza A enter the humans cell at the same time, an exchange of surface antigens between them occurs, which leads to the formation of new strains of the virus. Newly formed strains of viruses are very virulent and cause pronounced pandemics with a high degree of lethality. Exchange is possible between human and animal viruses. Genetic reassortment of the influenza pathogen can also occur in migrating wild birds with subsequent infection of poultry.

Influenza A virus is more virulent and contagious than influenza B and C viruses. It causes epidemics and pandemics. This is due to the fact that the human influenza A virus contains 2 varieties of neuraminidase (NA1, NA2) and 3 - hemagglutinin (HA1, HA2, HA3), while the B virus contains 1HA and 1NA, respectively, so it only has different serotypes within itself species Virus C contains only one type of hemagglutinin and does not contain neuraminidase. Antigen variability is very high in influenza type A virus (shift and drift). Duration of immunity is 1-2 years. Circulation of all influenza A virus subtypes is maintained among waterfowl. Influenza A virus is the most virulent and pathogenic to humans of the three serotypes and can cause more serious illness.

Influenza A virus is the most virulent and pathogenic to humans of the three serotypes and can cause more serious illness. There are several varieties of the influenza A virus. Those that have been found in humans: the least documented pandemic of 1889 (H3N8), known as the "Russian flu" [350], followed by the "Spanish flu" of 1918 (H1N1), the "Asian flu" of 1957 (H2N2). ), the "Hong Kong flu" in 1968 (H3N2), and the most recent pandemic of 2009 (H1N1), known as "swine flu". It should be noted that the most famous influenza pandemic, the Spanish influenza of 1918, and the most recent pandemic, the swine influenza of 2009, were caused by the H1N1 virus [351].

The Spanish influenza that caused a pandemic in 1918-1919 was caused by the H1N1 virus. The consequences of the pandemic were the death of about 40 million

people. Clinical symptoms and pathological manifestations were mostly limited to the respiratory tract and became the cause of almost 50% of deaths, besides, a significant proportion of the dead was in the age group of 20-40 years. Since scientific laboratories do not have isolates of the H1N1 virus, the biological properties of the virus that caused the Spanish group pandemic are not completely understood. The study of lung tissue samples made it possible to determine the gene sequences of the 1918 influenza virus and indicate an "unusual avian predecessor". The three-dimensional structure of the HA of the H1N1 virus that caused the 1918 influenza pandemic indicates that the hemagglutinin receptor has remnants of an avian progenitor, but has binding properties to human epithelial cell surface receptors Recent studies, with viruses created by reverse genetics that carry genes obtained from the influenza virus that caused the 1918 influenza pandemic, indicate increased virulence of the HA of this virus. Although these experiments were performed in laboratory animals, the infiltration of the lungs by inflammatory cells and the hemorrhagic pneumonia observed in these mice were signs of the disease in humans in the early stages of the 1918-19 influenza pandemic [352].

Genetic studies of other viruses that caused subsequent pandemics also suggest the combination of avian segments against human viral genes. For example, the influenza virus that caused the 1957 pandemic consisted of HA (H2), NA (N2) and a segment of the viral RNA polymerase gene, PB1 (polymerase base 1) was of avian virus origin, and other gene segments were derived from earlier circulating human virus. The influenza virus that caused the 1968 pandemic had avian HA (H3) and PB1 segments against human viral genes15,16. The acquisition of avian surface antigens allowed these viruses to bypass the human immune response [353]. Influenza pandemics are caused by viruses that possess an HA molecule to which most of the population lacks immunity. Recently, purely avian influenza viruses, including the H5N1, H9N2 and H7N7 subtypes, have been directly transmitted to humans, raising concern over the possibility of a new influenza pandemic among the world's immunologically naive populations. As the viruses responsible for pandemics in the past century were all characterized by the acquisition of HAs from avian viruses, with

the exception of the Russian influenza virus, clues to the molecular changes that give rise to human pandemic strains can be found in the avian reservoir [354].

The influenza B virus exclusively infects humans and birds and is less common than the influenza A virus. The duration of immunity in persons who have undergone an influenza B virus infection lasts 3-5 years. Due to the limited circle of circulation in nature, the antigenic variability of the influenza B virus is limited only to antigenic drift. It is less genetically diverse. The recombination of the influenza B virus with the influenza A virus leads to the development of epidemics.

The influenza C virus infects humans, dogs, and pigs. The absence of mutations means that a person gets influenza C almost once in a lifetime, and as a result, receives a long-lasting strained immunity to this type. An increase in the incidence of influenza C often precedes or accompanies epidemics of influenza A and B. By biological characteristics, virus C is more different from other members of the family of orthomyxoviruses. It is characterized by low reproductive activity in various cellular systems and the presence of receptors on the surface other than those of influenza A and B viruses. Receptor-destructive activity is not associated with neuraminidase, as in influenza A and B viruses, but with the enzyme neuraminate-0-acetylesterase.

The rapid spread of influenza epidemics is explained by: a short incubation period; variability of the virus; the presence of many types, subtypes, variants of the virus; ease of transfer; with general receptivity; short-term immunity. In temperate regions, seasonal influenza epidemics occur mainly in winter, while in tropical regions, influenza viruses circulate year-round, leading to less regular epidemics.

The entrance gate for the influenza pathogen is the cylindrical epithelium lining the tracheobronchial tree. In these cells, the first cycle of viral replication takes place, lasting about 4-6 hours. The avalanche-like release of mature virions is accompanied by massive cell death, which is clinically manifested by inflammatory phenomena of the respiratory tract and toxemia. The incubation period is short, ranging from a few hours to 1-2 days. Since the replication of the virus occurs in a geometric progression, an extremely high level of toxinemia is reached already on the 1st day of the disease.

Later, in connection with the necrosis of the epithelium and the destruction of the natural protective barrier, the virus from the places of primary localization quickly enters the bloodstream and internal organs with the development of viremia and generalization of the infection. The disease can be mild, sometimes asymptomatic, asymptomatic, moderate or extremely severe

The immunosuppressive effect of the influenza virus leads to the possibility of secondary infection, in particular in the respiratory system - the flu "opens the door" secondary microflora. Therefore, the flu can be accompanied by pneumonia caused by the addition of bacterial flora, mainly staphylococcal. Staphylococcal pneumonia is extremely severe, patients can die very early in the course of the disease. Accompanying chronic diseases can also become more active - tuberculosis, rheumatism, nephritis.

Immunity to influenza infection has been extensively studied and much of what is known is from a mixture of human and animal evidence [355]. Manish M.Patel et.al. [356] described less is known about the effect of immunity in preventing influenza infection versus attenuating illness, and immune correlates of illness attenuation. In a given individual, immunoattenuation is dynamic due to: innate, humoral, and cellular immune responses; responses at mucosal and systemic anatomical compartments; responses to homotypic and heterosubtypic viruses; time-varying immune responses that wane and are boosted by repeated exposures and vaccination; immunosenescence . Adaptive immunity is antigen-specific, stops viral replication and spread, eliminates virus-infected cells, and promotes tissue regeneration. Primary infection and vaccination generates acute and long-term adaptive immune responses through differentiation of naive cells into effector and memory cells. Acute infection is controlled by effector B cells that secrete antibodies and direct cellular responses by effector CD4 helper and CD8 cells; these acute adaptive responses stop replication and clear infection.

The formation of anti-influenza immunity takes place in several stages. 1st stage - activation of factors of non-specific protection (complement, phagocytosis, NK-killers), synthesis of interferon. Effects of IFN-α/β interferon: activation of genes with

direct antiviral activity; protective effect, when cells become immune to viral infection. When a cell is infected with viruses, interferon are synthesized in it. Interferon, which is released from a virus-infected cell, attaches to special receptors and the cell begins to synthesize antiviral proteins. IFN-γ has a positive effect on the activation of the cytotoxic action of NK cells in the foci of infection. The cytotoxic effect of NK-lymphocytes is formed already on the 2nd day after infection.

The 2nd stage is the formation of specific cellular and humoral immunity, which is directed against a certain strain of the virus. There are two types of immunological reactions: against the virion - mostly humoral immunity; impact on a virus-infected cell (these immune reactions are implemented through the coordinated action of various subpopulations of T-lymphocytes). Neutralization of the virus, preventing its attachment to epithelial cells, is carried out by different classes of immunoglobulins. Namely: IgG in the extracellular fluid; IgM in the blood; secretory IgA on the surface of mucous membranes. Immune complexes containing the influenza virus can bind complement, which helps neutralize the virus. The appearance of new influenza virus strains, even with a slight drift of surface antigens, significantly reduces the effectiveness of both post-infectious and post-vaccination immunity. When antigens shift, a new subtype of the virus is formed, against which the immunity formed against other "old" subtypes of the influenza virus is not effective.

The scientific publication Claudia Maria Trombetta et.al. [357] states, that children younger than 5 years old, and especially younger than 2 years old, have a higher risk of developing serious complications related to the flu. Children can also play a key role in the spread of influenza infection by shedding the virus in greater amounts and for longer than adults.

Although the flu can be serious and can affect anyone, adults over the age of 65 have a higher risk of developing serious flu-related complications than younger, healthy adults. In recent years, 70% to 85% of seasonal influenza-related deaths and 50% to 70% of hospitalizations have occurred among subjects aged ≥65 years, defined as the elderly. Vaccination is therefore strongly recommended for the elderly to prevent the disease and related complications.

The main methods of prevention and treatment of influenza include vaccination, passive immunoprophylaxis and antiviral chemotherapy.

Vaccination is a method of specific prevention of influenza, which is carried out with live (LAIV) and inactivated (IIV) vaccines.

Live (attenuated) vaccines contain live attenuated (weakened, devoid of virulence) strains of viruses.

Inactivated vaccines are obtained by exposure to microorganisms chemically or by heating. There are whole-virion, split and subunit inactivated vaccines. Whole-virion vaccines contain a purified mixture of inactivated whole viruses and are characterized by high reactogenicity. Split vaccines contain a purified mixture of all virus structures, they are characterized by higher immunogenicity and lower reactogenicity compared to whole-virion vaccines. Subunit vaccines contain only surface antigens of influenza viruses, have the highest degree of purification from impurities and are characterized by the lowest reactogenicity compared to other influenza vaccines.

The effectiveness of vaccination against the influenza virus is 75-90%. While influenza vaccines can be highly effective in adults, there are reduced benefits in young children leaving them vulnerable to infection [358].

WHO annually publishes recommendations on which influenza viruses should be included in influenza vaccines for use in the next epidemic season. WHO recommendations for the inclusion of viruses in annual seasonal vaccines are based on surveillance by the Global Influenza Surveillance and Response System ( GISRS), which plays a key role in global influenza risk assessment and conducts year-round virological surveillance. Based on GISRS surveillance, WHO has recommended appropriate viruses for inclusion in annual seasonal vaccines since 1973. Since 1998, the GISRS has provided biennial recommendations for the composition of seasonal influenza vaccines for the northern and southern hemispheres.

The GISRS network is a global system of health care facilities, whose activities are coordinated by WHO. Currently, it includes 148 National Influenza Centers (NICs), 7 WHO Collaborating Centers (CCs) on influenza, 4 WHO Core Regulatory

Laboratories (ERLs) and 13 Reference Laboratories (H5). When GISRS was established in 1952, only 25 countries had ongoing influenza surveillance and could report to WHO. Currently, more than 127 countries, regions and territories participate in GISRS activities [359].

If, in 2014-2019, GISRS processed an average of 3.4 million samples, over the past two years this figure has increased to 6.7 million samples, in addition, these laboratories have conducted 44.2 million tests for SARS-CoV-2 . GISRS members submit approximately 20,000 influenza virus samples to the WHO Central Committee each year and regularly update weekly influenza information based on laboratory and surveillance reports through the FluNet and FluID systems.

Such activity allows WHO to disseminate risk assessments in a timely manner and notify countries of changes in the epidemic situation from viral infection to influenza. GISRS operates year-round, allowing it to function as a global alert for emerging influenza and other respiratory viruses of public health importance[12].