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INFLUENZA VIRUSES-VIRUSES FOR ALL TIME

VIRRUSI INFLUENCE-VIRUSI ZA SVA VREMENA

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Apstrakt

Virusi influence izazivaju akutnu respiratornu bolest, poznatu kao influenza ili grip, kod ljudi i životinja od davnih vremena. Virusi inflence izazivaju epidemije svake godine i pandemije posle nekoliko decenija. Virusi inflenca su podeljeni i tipove A,B i C. Grip je ozbiljna respiratorna bolest koja može dati komplikacije pa je potrebna hospitalizacija ili uzrokuju smrt.
Razumevanje virusnih mehanizama će doprineti boljem lečenju i razvoju efikasnih vakcina za različite varijantne virusa koje će se koristiti u svetu.
Ključne reči: Virusi influence, grip, vakcina, pandemija

Ključne reči/Key words
Influenza viruses, flu, vaccine, pandemic

INTRODUCTION

Influenza, or flu, is a respiratory infection caused by several flu viruses. Influenza viruses are divided into three types designated A,B and C based upon their protein composition.

Influenza viruses types A and B are responsible for epidemics of respiratory illness that occur almost every winter. Influenza type A viruses are found in many kinds of animals, including ducks, chickens, pigs, and whales, and also humans. The type B widely circulates in humans.Influenza viruses type C usually causes either a very mild respiratory illness or no symptoms; it does not cause epidemics and does not have the severe public-health impact as influenza viruses types A and B. Type C has been found in humans, pigs, and dogs and causes mild respiratory infections, but does not spark epidemics.

Type A influenza is the most frightening of the other. It is belives responsible for the global outbreaks of 1918, 1957 and 1968, and now 2009.

Flu is important disease because it can cause serious complications. For elderly people, newborn babies, and people with certain chronic illnesses, however, the flu and its complications can be life-threatening.

Influenza viruses cause epidemics every few years, and pandemics every few decades. It results 250.000 - 500.000 deaths, and about 3 - 5 million cases of severe illness each year worldwide, with 5 -15% of the total population infected(1,2).

There are different terms for flu:

1/Seasonal flu is the term used to refer to the flu outbreaks that occur yearly, mainly in the late fall and winter.

2/Pandemic flu refers to particularly virulent strains of flu that spread rapidly from person to person to create a world-wide epidemic (pandemic).

3/Avian flu or bird flu occurs in wild and domestic birds. It does not normally spread from birds to humans. In 1997. for the first time, scientists found that bird influenza akipped the pig step and infected humans directly.

4/Swine flu does not normally infect humans, although sporadic cases do occur - usually in people who have close contact with pigs. Human to human transmission of swine flu is though to spread in the same way as seasonal flu - through coughing and sneezing. Pandemic of swine flu began in 2009(3,4,5).

VIRUS

Influenza viruses belong to family Orthomyxoviridae. The Orthomyxoviridae are family of RNA viruses that includes five genera: Influenzavirus A, B and C, Isavirus and Thogotovirus.

Influenza viruses are enveloped viruses with a segmented genome . They are spherical or filamentous in structure, ranging from 80 to 120 nm in diameter. Viruses contain linear negative-sense single stranded RNA. The total genome lenght is 12000-15000 nucleotides.

The genome of influenza A and B viruses consist of 8 separate segments and influenza C 7 segments covered by the nucleocapsid protein. Together these build the ribonucleoprotein (RNP). And each segment codes for a functionally important protein:

polymerase B1, B2, A protein, haemagglutinin, neuraminidase, nucleocapsid and matrix protein and non-structural protein.

Lipoprotein membrane enclose the nucleocapsid. They have helical symmetry.

The main antigenic determinants of influenza viruses A and B are the haemagglutinin (H) and neuraminidase (N) transmembrane surface glycoproteins.

There are 16 types of H antigen and nine types of N antigen, and there are many subtypes of each type. From time to time a virus emerges with a new combination of H and N genes formed by reassortment, and causes a pandemic.

Normally humans are infected only with viruses that have H type 1, 2 and 3 nad N type 1 or 2. H is the major antigen for neutralising antibodies, and is involved in the binding of the virus to host cell receptors. N is concerned with the release of progeny virions from the cell surface. Currently, only viruses of the H1N1 and H3N2 subtypes are circulating among humans.

The full nomeclature for influenza virus isolates requires connotation of the influenza virus type (A and B), the host species (ometted if human in origin), the geographical site, serial number, year of isolation, the H and N variants, for example: A/goose/Guangdong/1/96(H5N1).

Influenza virus is one of the most changeable of viruses. These genetic changes may be small and continuous or large and abrupt. Small changes are called antigenic drift.Antigenic drift occurs as result of point mutations in influenza viruses and reffers to minor, gradual, antigenic changes in H or N protein. The large changes are called antigenic shift. These changes occurs when two different flu strains infect the same cell and exchange genetic material. The novel assortment of HA and NA proteins in a shifted virus creates a new influenza A subtypes. Because people have little or no immunity to such a new subtypes, their appearance tends to coincide with a very severe flu epidemic or pandemic(1,6).

EPIDEMIOLOGY

In nature, the flu virus is found in wild aquatic birds such as ducks and shore birds. It has persisted in these birds for millions of years and does not typically harm them. But the frequently mutating flu viruses can readily jump the species barrier from wild birds to domesticated ducks and then to chickens. From there, the next stop in the infectious chain is often pigs. Pigs can be infected by both bird(avian) influenza and the form of influenza that infect humans. If a pig is infected with avian and human flu simultaneously the two virus may exchange genes. Such a ”reassorted” flu virus can sometimes spread from pigs to people.

In 1997. for the first time, scientists found that bird influenza skipped the pig step and infect human directly. But, fortunately the virus could not pass between people(7).

The ”swine flu”(mexican, new flu) pandemic of 2009. is caused by a novel influenza A virus designated H1N1 based upon its surface protein types. The virus was originally referred to as ”swine flu” because many of the genes in this new virus were very similar to influenza viruses that normally occur in pigs in North America. However, the new virus is different from the typical swine flu viruses found in pigs. It contains genetic material that is typically found in stains of the virus that affect humans, birds and swine.

The new strain appears to be a recombinant between two older strain. Preliminary genetic charasterization found that the hemagglutinin gene was similar to that of swine flu viruses present in US pigs since 1999, but neuraminidase and matrix protein genes resembled versions present in European swine flu isolates.

The novel H1N1 virus first caused illness in Mexico and the United States in March and April 2009. In March and April 2009. more than 1000 cases of swine flu in humans were detected in Mexico, and more than 80 deaths.

Influenza is primarly transmitted from person to person via dropelts (?5μm in diameter) from nose and throat of an infected person who is coughing and sneezing. Transmission may also occur through direct skin-to-skin contact or indirect contact with respiratory secretions (touching contaminated surface then touching the eyes, nose or mouth). Individuals may spread influenza virus from up to two days before to approximately 5 days after onset of symptoms. Children can spread the virus for 10 days or longer.

Within nasal secretions, millions of virus particles per ml are shed, so that a 0.1μl aerosol particles contains more than 100 virus particles. A single human infectious dose of influenza virus might be between 100 and 1000 particles.

As influenza viruses are normally highly species specific. This is due to differences in the use of cellular receptors.

The main targets of influenza virus are columnar epithelial cells of the respiratory tract. These cells may be susceptible to infection if the viral receptor is present and functional. Thus, viral receptors are determinants of tropism.In influenza infection, the receptor binding site of viral hemagglutinin(H) is required for binding to galactose bound sialic acid on the surface of host cells.

The influenza virus binds to the cell surface by fixing the outher top of the H to the sialic acid of a cell glycoproteins and glycolipids.

Avian influenza viruses bind to cell-surface glycoproteins containing sialyl-galactosyl residues linked by a 2-3 linkage, whereas human and swine viruses bind to receptors that contain terminal 2-6linked sialyl-galactosyl mioeties(8).

The time from entry to production of new virus is on average 6h.

Flu viruses can remain infectious for about one week at human body temperature, over 30 days at O^{O}C and indefinitely at very low temperature. They can be inactivated easily by disinfectants and detergents

When any new strain of flu emerges that acquired the ability to pass from person to person, it is monitored very closely in case it has the potential to spark a pandemic.

During the 20th century, the emergence of new influenza A virus subtypes caused three pandemics.

1918 ”Spanish flu” -The Spanish flu pandemic remains the most devastating outbreak of modern times. Caused by a form of the H1N1 strain of flu, it is estimated that up to 40% of the world, s population were infected, and more than 50 million people died, with young adults particularly badly affected.

1957 ”Asian flu”, Asian flu killed two millions people. Caused by a human form of the virus, H2N2, combining with a mutated strain found in wild ducks. The elderly were particularly vunerable.

1968 ”Hong Kong flu”-An outbreak first detected in Hong Kong, and caused by a strain known as H3N2, killed up to one million people globally, with those over 65 most likely to die.

2009. Mexican, swine or new flu started first pandemic in 21th century(9,10,11,12).

LABORATORY DIAGNOSIS

For laboratory diagnosis different virological as well as serological methods are available.

For early diagnosis of acute influenza virus infections, virus detection using rapid procedures for virus isolation or antigen staining and molecular biological techniques have been developed.

Virus isolation is regarded as the ”gold standard” among the different methods for virus detection.Virus isolation is a techique whereby a specimen is inoculated in a live culture system: embryonated eggs or tussue culture.Specimens are inoculated into amniotic cavity of 10-12 day embryonated chiken eggs. Various cell-lines are utilised to isolate influenza viruses, most commonly Madin-Darby canine kidney (MDCK) cells. Virus culture provides results in 2-10 days.

Rapid antigen assays (most of which work on an EIA or immunochromatography principe) enable the diagnosis of influenza within 10-30 minutes. In these tests, viral antigen is separated chromatographically and detected immunologically by a color reaction.

Molecular biological methods are the amplification of viral genome by the polymerase reaction (PCR) and real-time PCR. These techniques are still rather axpensive, but may provide a result after 2-3 h.RT-PCR can only be performed in well equipped laboratory facilities by trained personnel.RT-PCR is a process whereby RNA is first converted to complementary DNA (cDNA) and a section of the genome is then amplified through the use of primers that bind specifically to this target area.

About 1 week after onset of clinical symptoms, a specific immune reaction becomes demonstrable.

Different serological techniques are available for influenza diagnosis.Conventional methods for antibody detection are the complement fixation test (CFT) and the hemagglutination inhibition (HAI) test. Viral nucleoprotein (NP) or hemagglutinin (HA) serve as antigens. Awereas the conserved NP antigen used in the CFT allows the detection of type-specific influenza antibodies, subtype-specific antibodies can be determined by means of the HAI test. In this way, serological findins may complement the results of virus detection.

As part of an automated serology, both IFT and ELISA are widely used methods for determination of type-, but not subtype-specific antibodies The detection of IgG antibodies is only useful to exclude an influenza infection, virus-specific IgM or IgA antibodies are indicative of recent infections(1,13).

Serological diagnosis has little value in diagnosing acute influenza. It may have value in diagnosing recently infected patients.Serology is also used to determine the response to influenza vacination.

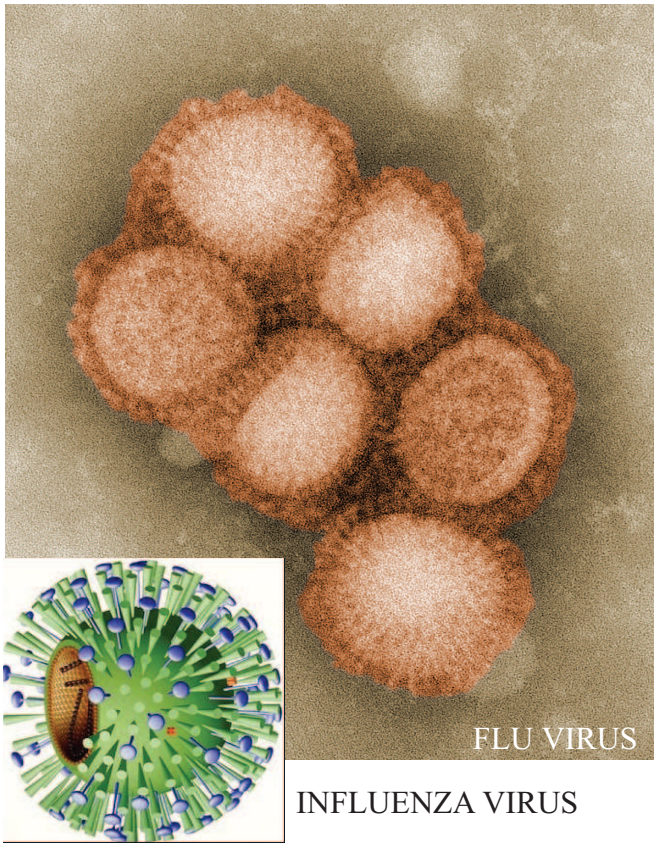
ANTIVIRAL DRUG

Four different influenza antiviral drugs (amantadine, rimantadine, oseltamivir, and zanamivir) are approved for the treatment and/or prevention of influenza.

In the case of a future pandemic, antiviral drugs may play an important role in the early phase, when vaccines against the new strain are not yet avaiable or as long as the avaiable vaccine is in short supply.

All drugs are most effective if started within a few hours of the onset of symptoms and are generally licensed for use within 48 hours of the first symptoms. They can modify the severity of illness, as well as reducing the intensity of influenza symptoms and decreasing the duration of illness by about 1 to 3 days.

The recommended duration of treatment for both drugs is 5 days



INFLUENZA VIRUS

The older drugs, rimantadin and amantadine, M2 inhibitirs block an ion channel formed by the M2 protein. These drugs are only effective against influenza A virus (influenza B does not possess M2 protein). Amatadine and rimatadine have more side effects than neuraminidase inhibitors, and may select for readily transmissible drug-resistant viruses.

Point mutations in the M gene lead to amino acid changes in the transmembrane region of the M2 protein end may confer high-level resistance to amantadine.Global prevalence of adamantane-resistant influenza viruses was found to have significantly increased from 0.4% in 1994-1995 to 12.3% in 2003-2004.

The new drugs, Oseltamivir and zanamivir are neuraminidase inhibitors.When exposed to neuraminidase inhibitors, the influenza virions aggregate on the surface of the host cell, limiting the extend of infection within the musosal secretions and reducing viral infectivity.

Oseltamivir and zanamivir seem to have similar efficacy, but they differ in their modes of deliver and tolerability. Zanamivir is delivered by inhalation and is well tolerated; oseltamivir is taken in the form of a pill but may produce nausea and vomiting in some patients.

The neuraminidase inhibitors, oseltamivir and zanamivir, have fewer side effects that the M2 ion channel inhibitors rimatadine and amantadine, and drug resistance seems to develop less frequently (14,15).

Antibiotic tretment should be reserved for the treatment of secondary bacterial pneumonia.

VACCINE

There are different types of vaccine for influenza: killed and lived vaccines. Other types of vaccine are in development, where a degree of genetic manipulation is involved(16,17).

1/ Killed vaccines can be divided into whole virus vaccines, and split or subunit vaccines.

Whole virus vaccines were the first to be developed. Influenza virus was grown in the allantoic sac of embryonated hen,s eggs, subsequently purified and concentrated using red blood cells, and finally inactivated.These vaccines are safe and well tolerated, with an efficacy of 60- 80% in children and adults.

Split vaccines are produced in the same was as whole virus vaccines, but virus particles are disrupted using detergents.

Subunit vaccines consist of purified H and N proteins, with the other viral components removed.

Split and subunit vaccines cause fewer local reactions than whole virus vaccines, and a single dose produces adequate antibody levels in population exposed to similar viruses.

2/Live attenuated influenza vaccines have been in use for several years in the former Soviet Union and USA. It consists of a master attenuated virus into which the H and N genes have been inserted.It is cold-adapted for intranasal administration.

The nasal-spray flu vaccine or live attenuated influenza vaccine was first lincesed in 2003. In healthy adults, efficancy after one dose of vaccine ranges from 80-100%, and in other population is lower.

Side effects of vaccine include soreness at the side of the injection, muscle aching, fever, and feeling unwell and also manifestations of egg allergy.

The most dangerous side effect of influenza vaccine is Guillain-Barre sindrome but is rare.Guillain-Bare syndrome(GBS) is an illness characterized by fever, nerve damage, and muscle weakness. In 1976.vaccination with the swine flu vaccine was associated with development of GBS(1).

Vaccination against the prevalent wild-type influenza virus is recomended for all individuals in high-risk groups, including those aged 65 years or older, and those with chronic illness, particularly diabetes, chronic respiratory and cardiac disease, and persons immunocompromised from disease or concomitant therapy. In addition, it is generally recommended that all healthcare personnel be vaccinated annually against influenza.

The vaccine is generaly effective against the influenza virus within two weeks of administration(18). The vaccine is only effective against the strains of the virus that mutch the vaccine. These strain vary from flu season to flu season each year.

A vaccine against the novel H1N1 flu is in production as of summer 2009 and may be ready for administration in fall of 2009.

Vaccination against influenza is a crutial weapon, in fight against seasonal influenza, and also against a pandemic.

Abstract

Influenza viruses are the cause of outbreaks of acute respiratory disease, known as influenza or flu, which has afflicted man and animals since ancient times.

Influenza viruses cause epidemics every few years, and pandemics every few decades.Flu viruses are classified as types A, B and C. Flu is a serious respiratory illness which can be debilitating and cause complications that lead to hospitalisation and death.

The knowledge about the viral mechanisms will facilitate the development of better treatment option and more effective vaccines to be distributed worlwide against present and future influenza virus variants.

REFERENCES

1.Wright PF, Neumann G and Kawaova Y. Orthomyxoviruses. In Fields Virology, Fifth Ed, 2007, Philadelphia, 1691-1740.

2.Cox NJ, Subbarao K. Global epidemiology of influenza: past and present. Ann Rev Med 2000;51:407-21.

3.De Jong MD, Hien TT. Avian influenza A (H5N1). J.Clin Virol.2006;35:2-13.

4.Blumenshine P, Reingold A, Egerter S, Mockenhaupt R, Braveman P and Marks J. Pandemic Influenza palnning in the United States from a health disparities perspective. Emerg Infect Dis 2008; 14:5:709-719.

5.Beigel JH, Farrar J, Han AM et al. Avian influenza A (H5N1) infection in humans. N Engl J Med 2005; 353:1374-85.

6.Wagner R, Matrosovich M, Klenk HD. Functional balance between haemagglutinin and neuraminidase in influenza virus infections. Rev Med Virol 2002;12:159-66.

7.Monto AS. The treat of an avian influenza pandemic. N Engl J Med 2005;352:323-5.

8.Ito T, Suzuki T, Takada A et al. Differences in sialic acid-galactose linages in the chicken virus receptor specificity and variant selection. J Virol 1997;71:3357-62.

9.Ferguson NM, Cummings DA, Fraser C, Cajka JC, Cooley PC, Burke DC. Startegies for mitigating an influenza pandemic. Nature 2006;442;448-52.

10.Belshe RB. The origins of pandemic influenza-lessons from the 1918 virus. N Engl J Med 2005;353:2209-11.

11.Horimoto T and Kawaoka Y. Influenza: lessons from past pandemics, warnings from current incidents. Nature Rev. Microbiol; 2005; 3, 591-600.

12.Cuevas M, Curley A, Hellerman C, Quijano E, Candiotti S (25 April 2009). More cases of swine flu reported; WHO warns of health emergency.http:www.cnn.com/2009/Health/04/25/swine.flu/index.html.

13.Allwinn R, Preiser W, Rabenau H, BuxbaumS, Sturmer M, Doerr HW. Laboratory diagnosis of influenza-virology or serology? Med Microbiol Immunol 2002; 191:157-160.

14.Moscona A. Neuraminidase inhibitors for influenza. N Engl J Med 2005;353:1363-73.

15. Lackenby A, Hungnes O, Dudman SG, Meijer A, Paget WJ, Hay AJ, et al. Emergence of resistance to oseltamivir among influenza A (H1N1) viruses in Europe. Eurosurveillance.2008;13 (cited 2008 Jul 11). Available from http://www.eurosurveillance.org/edition/v13n05/080131_2.asp

16.Fedson DS. Preparing for pandemic vaccination: an internatinal policy agenda for vaccine development. J public Health Policy 2005;26:4-29.

17.Blendon RJ, Koonin LM, Cetron MS, Pollard WE, Mitchell EW, Weldon KJ, Herrmann MJ. Public response to community mitigation measures for pandemic influenza. Emerg infect Dis 2008; 14:5:778-786.

18.Johnson PR, Feldman S, Thompson JM, Mahoney JD, Wright PF. Immunity to influenza A virus infection in young children: a comparison of natural infection, live cold-adopted vaccine, and inactivated vaccine. J Infect Dis 1986;154:121-7.

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