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Influenza: An overview

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Abstract

Seasonal influenza viruses in tropical regions may occur throughout the year, causing outbreaks and epidemics more regularly in humans. There are four types or large groupings of seasonal influenza viruses; Influenza A, B, C, and D, but only influenza A and B viruses cause clinically important human disease and seasonal epidemics. It can cause mild to severe illnesses and even deaths, particularly in high-risk individuals. Vaccination is the most effective means of preventing influenza and its complications. Among healthy adults, influenza vaccine provides protection, even when circulating viruses may not exactly match the vaccine viruses. In elderly, it reduces severity of disease and incidence of complications and deaths. Vaccination is especially important for people at higher risk of serious influenza complications, and for people who live with, care for, high risk individuals.

Keywords: Influenza, Antivirals, Inactivated vaccines, Live attenuated influenza vaccine

Seasonal influenza

Seasonal influenza viruses circulate and cause disease every year in the winter months in temperate climates. In tropical regions, it may occur throughout the year, causing outbreaks and epidemics more regularly in humans. Seasonal influenza can cause mild to severe illnesses and even deaths, particularly in high-risk individuals. These viruses evolve continuously due to accumulation of point mutations in genes coding for antibody binding sites leading to emergence partially related new strains developed from only one virus strain.[1] Thus, the people can get infected multiple number of times in form of outbreaks and epidemics throughout their lives. Therefore, components of influenza virus vaccine are reviewed frequently and updated periodically to ensure continued supply of effective vaccine.[2]

There are four types of large group of seasonal influenza viruses; Influenza A, B, C, and D, but only influenza A and B viruses cause clinically important human disease and seasonal epidemics.[3,4,5] Though type C infects humans of all ages, but tends to cause mild illness and is associated with sporadic cases and minor localized outbreaks.[6] Little known about type D, which does not cause human disease and mainly infects pigs and cattle.[7] Type A influenza viruses are further classified into subtypes on the basis of specific variety and combinations of surface proteins, the heamagglutinin or 'H' and the neuraminidase or 'N', antigens. To date, 18 heamagglutinin subtypes and 11 neuraminidase subtypes have been identified, but only three heamagglutinin subtypes (H1, H2 and H3) are recognized to epidemics in humans.[1] Nomenclature includes the virus type and subtype, natural host species, geographical origin, year of isolation, and strain number (Such as H1N1/A/duck/Alberta/35/76).[8] Currently, influenza A(H1N1) and A(H3N2) are the circulating influenza subtypes. The seasonal A(H1N1) that caused the 2009 influenza pandemic, is now circulating seasonally. In addition, there are two type B viruses that are also circulating as seasonal influenza viruses, divided into lineages on the basis of the heamagglutinin glycoprotein and are named after the areas from where they were first identified B/Victoria and B/Yamagata lineages. Influenza B viruses are not classified as subtypes. It mainly infects humans and children are affected at a disproportionately higher rate among the general population.[9,10]

Pandemic Influenza

When influenza A virus which was not previously circulating among humans, a pandemic occurs to which most people do not have immunity. Some pandemics may result in large number of severe infections or some may have milder infections. Pandemic influenza is due to sudden major change virus antigenicity resulting from one or more virus strains (genome resortment) which occurs occasionally, irregularly and unpredictably. The most dreaded pandemic was the "Spanish flu" in 1918-1919 which caused an estimated 20-30 million deaths worldwide. In 2009, a strain of influenza A(H1N1) virus which had never seen before caused the 2009 H1N1 pandemic. Currently, there is no longer a pandemic virus circulating in the world.[11]

Zoonotic or variant influenza

Humans are also affected with influenza viruses that are routinely circulating in animals such as avian influenza virus subtypes A(H5N1) and A(H9N2) and swine influenza virus subtypes A(H1N1) and A(H3N2). Other animals including horses and dogs also have their own varieties of influenza viruses. All these animal viruses are distinct from human influenza viruses and do not easily transmit between humans. Sometimes it

may occasionally infect humans through direct contact with infected animals or contaminated environments, and do not spread very far among humans. However, if such a virus acquired capacity to spread easily among either through adaptation or acquisition of certain genes from human viruses, it could result in an epidemic or pandemic. Over the last decades, there have been multiple reports of sporadic transmission of influenza viruses among animals and humans. When viruses of subtype A(H3N2) circulating in swine, infected people in the USA in 2011, they are labeled as 'variant' (with a 'v' placed after the name of the virus) in order to distinguish from human viruses of the same subtypes.[12] The variant terminology is also used for other non-seasonal influenza viruses, particularly viruses of H1 and H3 subtypes circulating in swine, when viruses are detected in humans.[12] Other animal viruses i.e., avian influenza A(H5N1), A(H7N7), A(H7N9) and A(H9N2), infecting people are called "avian influenza" or "zoonotic influenza" viruses.[13] As such the term "swine flu" refers to swine influenza viruses infecting swine, and is never used when such viruses infect people.[11]

Seasonal epidemics and Signs and Symptoms

In temperate climates, seasonal epidemics occur mainly during winter, while in tropical regions, influenza may occur throughout the year, causing irregular outbreaks. Worldwide annually, there are approximately one billion people are infected resulting in about 2-3 million cases of severe illness, and about 500,000 deaths.[5] Research estimates indicate that 99% of deaths in children under 5 years of age with influenza related lower respiratory tract infections are found in developing countries.[14] Seasonal influenza spreads easily, in crowded areas including schools and nursing homes. When the infected persons cough or sneeze, droplets containing viruses are dispersed into the air and are spread to persons in close proximity. The virus also can spread by hands contaminated with influenza viruses.

Influenza is characterized by sudden onset of fever, dry cough, headache, malaise, myalgia, sore throat and nasal congestion.[15,16] Gastroinstinal symptoms including nausea, vomiting and diarrhea are also common.[17] The incubation period is 1 to 4 days.[18] Viral shedding usually occurs from one day before onset of symptoms, to 5-7 days after.[19,20] Mortality is higher among high-risk individuals with complicated influenza (illness necessitating hospital admission, or an exacerbation of an underlying chronic illness) across all age groups, but is highest in infants aged 6 months or younger.[21,22]

Diagnosis

Most influenza is diagnosed clinically in the community at times when the virus is known to be circulating. Patients admitted to hospital may have respiratory samples (throat swabs and nasal swabs) taken for testing by polymerase chain reaction (PCR), rapid antigen test or immunofluorescence assay.[1]

Treatment

Antiviral drugs for influenza may reduce severe complications and deaths.[23,24] World health organization recommends treatment of suspected and confirmed influenza for individuals at risk of complicated influenza.[25] Ideally, they need to be administered early (within 48 hours of onset of symptoms) in the disease without awaiting the result of investigations.[26]

Therefore, 2 classes of antiviral are available:

1. Inhibitors of the influenza neuraminidase protein (oseltamivir and zanamivir; as well as peramivir and laninavir) which inhibits release of virions from infected cells and reduce the rate of viral replication. WHO recommends neuraminidase inhibitors as the first-line treatment.[2]
2. M2 proton channel blockers adamantanes (amantadine and rimantadine) to which virus resistance have been frequently reported, thus currently not used for treatment.

WHO also monitors antiviral susceptibility among circulating influenza viruses.[2]

Prevention

Vaccination is the most effective means of preventing influenza and its complications. Among healthy adults, influenza vaccine provides protection, even when circulating viruses may not exactly match the vaccine viruses. In elderly, it reduces severity of disease and incidence of complications and deaths. Vaccination is especially important for people at higher risk of serious influenza complications, and for people who live with, care for, high risk individuals. WHO recommends annual vaccination for: pregnant women at any stage of pregnancy, children aged between 6 months to 5 years, elderly individual (aged more than 65 years), individuals with chronic medical conditions (for example, chronic heart, lung, kidney, liver, neurological, and metabolic diseases, such as diabetes) and health care workers.[2]

Influenza vaccine is most effective when circulating viruses are well-matched with vaccine contained viruses. Because of changes in circulating strains, antigenic drift, and waning antibody, immunity developed in one influenza season may not provide protection in future years. Thus influenza vaccine are updated half yearly or annually to include the viral strains that are predicted to circulate in coming winter.[27,28]

WHO has updated its recommendation on the composition of the inactivated vaccine that targets the three most representative virus types in circulation (two subtypes of influenza A virus and one influenza B virus). Starting with the 2013-2014 northern

hemisphere influenza season, a fourth component (second influenza B virus) is recommended to support qudrivalent vaccine development.[2] This inactivated qudrivalent vaccine is expected to provide wider protection against influenza B virus infections. A number of inactivated and recombinant influenza vaccines are available in injectable form. Studies have shown that inactivated influenza vaccines cannot cause influenza disease and are safe in pregnancy.[29,30] Common side effects of vaccination include local injection site reactions and cold-like symptoms. Fever, malaise and myalgia are less common.[31] Contradictions include confirmed severe allergic reaction (anaphylaxis) to a previous influenza vaccine or to any component of vaccine.[21]

Live attenuated influenza vaccine (LAIV) is also available in form of nasal spray. Attenuated live nasal spray formulation is recommended in children aged 2 to <17 years based on its superior efficacy and greater immunity against mismatched strains compared with inactivated vaccines.[32,33,34] It should not be given to children, adults and pregnant women with immunosupression or to those taking salicylate treatments because of risk of Reye's syndrome.[21]

Due to constant evolving nature of influenza viruses, the WHO Global Influenza Surveillance and Response System (GISRS) – a network of 143 National Influenza centres (NICs), 6 WHO collaborating centres (CCs), 4 WHO Essential Regulatory Laboratories (ERLs) and 13 WHO H5 Reference Laboratories around the world continuously monitors the influenza viruses circulating in humans and updates the composition of influenza vaccines twice a year.[35] In 2016, NICs collected and tested up to three million clinical specimens from patients and shared representative influenza viruses with the WHO CCs for detailed analyses and for making recommendations for vaccine composition.[35]

WHO recommends that influenza vaccines for use in the 2017-2018 northern hemisphere influenza season contain the following viruses: – an A/Michigan/45/2015 (H1N1)pdm09-like virus; – an A/Hong Kong/4801/2014 (H3N2)-like virus; and – a B/Brisbane/60/2008-like virus.[35] The B/Brisbane/60/2008-like viruses are from the influenza B/Victoria lineage. It is recommended that quadrivalent vaccines contain the above three viruses and a B/Phuket/3073/2013-like virus, a B/Yamagata-lineage virus.[35] The A(H1N1)pdm09 virus has been updated compared to the virus recommended for northern hemisphere 2016-2017 influenza season. This updated recommendation is as follows: replacement of the A/California/7/2009 (H1N1)pdm09-like virus with an A/Michigan/45/2015 (H1N1)pdm09-like virus.[35] These recommendations are the same as those made for the 2017 southern hemisphere influenza vaccine.[35]

Influenza viruses circulate at varying times through the year with multiple peaks in tropical and sub-tropical countries. In selecting which vaccine formulation to use, these countries should consider their surveillance information, in particular epidemiological and virological data at both national and sub-national level to make evidence-based decisions on timing of vaccination campaigns and whether to use the formulation recommended for northern or southern hemisphere influenza season.[36] From an antigenic evolution perspective, there is no evidence to suggest the need for a 3rd recommendation for vaccine composition specifically for the tropics and subtropics, and the most recent WHO influenza virus vaccine recommendation should be used, independent of the hemisphere in which the country is situated.[36] Countries are encourage to strengthen surveillance and share viruses with WHO Collaborating Centers of Global Influenza Surveillance and Response System for analysis of antigenic and genetic similarity with both the northern hemisphere and southern hemisphere vaccine formulation of the respective season, to determine which vaccine formulation has a better antigenic correspondence with currently circulating viruses. A cartographic time-series analysis of antigenic evolution of the influenza A(H3N2) virus isolated between 2002 to 2006 in Thailand and a similar analysis for influenza B/Yamagata and B/Victoria lineage viruses from 17 other countries in the tropics and subtropics showed no substantial differences from the global patterns of antigenic evolution.[37]

Anti-viral chemoprophylaxis

Influenza may be prevented or rendered less severe by post-exposure prophylaxis (PEP) with anti virals i.e., oseltamivir and zanamivir and to be started within 48 hours and 36 hours of contact respectively.[38,39] National institute for health and care excellence (NICE) and Public Health England recommend that, when influenza is circulating, antivirals are offered to those who are: In at-risk groups, who have had close contact with people with confirmed or suspected influenza and have not received vaccination in the current influenza season, or who have been vaccinated < 14 days since contact or where there is significant mismatch between vaccine and circulating strains or during an outbreak in a closed setting regardless of vaccination history.[21,23]

Infection control and isolation

Hand and cough hygiene are important interventions to reduce influenza spread in the community, as well as in the close settings.[1] During an outbreak, residents of closed settings are isolated for the duration of the infectious period (five days after symptom onset) to limit spread to others. Cohorting of patients (i.e., in separate hospital bays or separate floors of a residential homes) may be necessary.[1] Residential homes may need to be closed to new admissions until the outbreak is controlled. Care must be taken when

discharging a patient from a ward with a known influenza outbreak to a care home; or vice versa.[1]

New developments in prevention and treatment of influenza

Vaccine candidates have recently been developed that can elicit antibodies against multiple influenza strains, and thus could overcome the need for annual influenza vaccines.[40,41,42] Several drugs are currently in development for influenza treatment, including favipiravir, nitazoxanide and arbidol.[43-47]

Conclusion

The transmission of pandemic influenza A(H1N1)2009 despite a novel strain exhibited important similarities with the transmission of seasonal influenza, to which the majority of the population had little preexisting immunity. In comparison with tropical and subtropical countries, the countries in temperate climates had higher peaks, shorter durations of pandemic activity, and higher proportions of A(H1N1)pdm09 among influenza A-positive samples.[48,49]

Influenza viruses are a constant threat to humanity. Syndrome and virological surveillance in both humans and animals to monitor the impact of newly introduced seasonal virus strains as well as sporadic introduction of animal and pandemic influenza viruses is of utmost importance for epidemic or pandemic preparedness.

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