INFLUENZA VIRUS:
Infections and Their Treatment

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ABSTRACT
Influenza virus is responsible for a number of pandemics. Its various subtypes have been identified such as H1N1, H2N2, H3N2, H3N2v, etc. that are responsible for infections like swine and bird flu. WHO has confirmed the incidences of bird-human infections in people who had a record of close contact to poultry. Similarly, human to human transmission can also take place. Various drugs have been employed to guard against these infections but recently some drug resistant strains of influenza virus have also been identified. Therefore, vaccines are found to be the most reliable source for the prevention of such flu infections. However, the right use of antiviral medicines, vaccines and public health interventions can result in better progress against the viral disease.

KEY WORDS: Influenza, pandemic, diseases control and preventions.

INTRODUCTION
Viruses having the H1N1, H2N2 and H3N2 combinations were responsible for the Spanish flu of 1918, the Asian flu in 1957 and Hong Kong flu in 1968, respectively. Influenza A virus of the H5N1 subtype has now been recognized in a human patient, thus raising debate about its potential to cause a new human influenza pandemic. On the contrary swine flu has stolen the attention from bird flu since it was first reported in April 2009, but still H5N1 virus is considered as a important threat to human health. Since November 2003, almost 400 cases of human infection with extremely pathogenic avian influenza A (H5N1) viruses have been reported in Asia, Africa, the Pacific, Europe and the Near East. By March 10, 2006, 97 people in Vietnam, Cambodia, Indonesia, Thailand, China, Turkey and Iraq had died from the infection. Concurrently, avian flu has killed millions of birds world-wide over the previous few years.

H3N2v: SWINE FLU
From 1990 to 2010, human infections with swine-origin influenza viruses were infrequent, and the US Centers for Disease Control and Prevention (CDC) established a total of only 27 cases through this period. Though, the number has been rising since 2011, as of August 31, 2012, a total of 309 cases have been reported. Study of viral RNA in clinical respiratory samples from 12 cases in 2011 exposed an alternate strain, called H3N2v, which is a hybrid including genetic material from swine H3N2 and the human virulent virus H1N1pdm09. The M gene in this innovative variant came from the human virus, whereas the further seven genes came from the swine virus when a host was infected with both viruses at the same time. As an outcome of this genetic re-assortment, this alternative virus is genetically and antigenically dissimilar from recurrent H3N2.

Epidemiologic information showed that children under 10 years of age are mainly at risk to this new variant because they are deficient in immunity, while adolescents and adults may have some immunity from cross-reacting antibodies. The majority of the swine infected people have found to be exposed in agriculture as well as in county and state fairs. Till to date, only partial human to human spread have been identified. In suspected cases, the clinician must inform the local or state public health department and recommend for a special test to be carried on respiratory samples, the CDC Flu Real-Time Reverse Transcriptase Polymerase Chain Reaction Dx Panel.

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Other diagnostic test like immunofluorescence analysis (direct fluorescent antibody staining) cannot exclusively observe H3N2v. The present seasonal influenza vaccine will not shield against H3N2v infection.

H5N1: THE THREATENING OF BIRD FLU PANDEMIC

Since 2003, influenza A H5N1, an extremely pathogenic avian virus, has killed more than 100 million birds in Asia, Middle East and Africa. On August 10, 2012, the World Health Organization (WHO) confirmed 608 cases of this virus in humans, of which 359 resulted in deaths. The majority infected patients had a record of close contact with diseased poultry. However, human-to-human transmission can also take place through very close, contact with a seriously ill patient. Molecular studies of this virus have exposed additional approaches into its pathogenesis. A few of the viruses isolated from humans showed mutations that allow them to attach to human-type receptors. Amino acid replacements in the polymerase basic protein 2 (PB2) genes are related with mammalian adaptation, virulence in mice, and viral replication at temperatures there in the upper respiratory tract. Elevated plasma levels of macrophage- and neutrophil-attractant chemokines and both anti-inflammatory and inflammatory cytokines (interleukin 6, interleukin 10, and interferon gamma) have been observed in patients by H5N1 infection. A recent study has reported that H5N1 causes major perturbations in the host’s protein synthesis machinery as early as 1 hour after infection, suggesting that this virus expand an early advantage in replication via the host’s proteome. If avian H5N1 and a human influenza virus substitute genes in a host for example swine, the novel hybrid virus will include genetic material from both strains and will have surface antigens that the human immune system does not identify. This might lead to a disturbing avian flu pandemic with increased death rate. An inactivated whole-virus H5N1 vaccine has been prepared by the US government to avoid H5N1 infection. For management, the neuraminidase inhibitor oseltamivir is the drug of choice. Oseltamivir resistance remains exceptional. Favorably, zanamivir is still effective against oseltamivir-resistant variants that have N1 neuraminidase mutations.

H1N1: THE LOOMING THREAT KILLING MOST OF PEOPLE

Around, 18,500 deaths have been reported worldwide due to H1N1 pandemic from April 2009 to August 2010. In another study, around 283,500 respiratory and cardiovascular deaths have been reported with this pandemic which is about 15 times greater. Several strains of influenza A virus are found to be inactive against amantadine and rimantadine, due to amino acid replacements in the M2 protein. Similarly, resistance to neuraminidase inhibitors such as oseltamivir and zanamivir has also been reported rarely. Most oseltamivir-resistant viruses have been isolated from immunocompromised hosts treated with oseltamivir. All the resistant viral isolates involved an amino acid substitution of histidine (H) to tyrosine (Y) at position 275 of the viral neuraminidase. Generally, spread of these oseltamivir-resistant strains has been partial and unsustained, but it can arise in settings of close contact, such as school camps hospitals or long train rides. Oseltamivir-resistant strains were noticed in lesser than 1% of isolates from the community through the 2010–2011 influenza season in the Northern Hemisphere and the majority countries in the Southern Hemisphere in the 2011 flu season. This was the primary information obtained from the community transmission of oseltamivir-resistant H1N1. It is a warning indication of the possibility for an extensive outbreak of this virus. In the incident of such an outbreak, inhaled zanamivir would be the only efficient treatment accessible.

TRIVALENT INACTIVATED VACCINE

The trivalent inactivated influenza vaccine for the 2012–2013 season includes three inactivated viruses: Influenza A/California/7/2009(H1N1)-like and Influenza A/Victoria/361/2011(H3N2)-like
Influenza B/Wisconsin/1/2010-like (Yamagata lineage). The influenza A H3N2 and influenza B antigens are dissimilar from those in the 2011–2012 vaccine.\textsuperscript{46} The H1N1 strain is derived from H1N1pdm09, which has been controlled in the 2011–2012 seasonal vaccine. This vaccine will not shelter against H3N2v or H5N1.

**LATEST RECOMMENDATIONS ON VACCINATION**

Since 2010, A Committee on Immunization Practices (ACIP) has suggested annual flu shots for all people older than 6 months in the United States.\textsuperscript{47} Vaccination should be completed before the start of influenza activity in the community. Though, one should keep on offering vaccination during the influenza season as long as influenza viruses are flowing in the community. Children of ages 6 months to 8 years who are not vaccinated earlier against influenza virus should obtain two doses of the vaccine for at least 4 weeks separately for an optimal immune response.\textsuperscript{48,49}

**RECOMMENDATIONS FOR PEOPLE ALLERGIC TO EGGS**

Influenza vaccines are prepared by growing the virus in chicken eggs. So, highly allergic and anaphylactic reactions can take place in people hypersensitive to eggs. The ACIP recommends that if people experienced only inflammation after egg exposure, they should still obtain the trivalent inactivated vaccine. The ACIP have reviewed this information from the Vaccine Adverse Event Reporting System.\textsuperscript{50-59}

In December 2009, the US Food and Drug Administration (FDA) licensed a novel trivalent inactivated influenza vaccine with elevated doses of hemagglutinin antigens for adults above the age of 65.\textsuperscript{60} Post licensure safety surveillance in 2010 found no severe safety concerns.\textsuperscript{61}

**LIVE-ATTENUATED INFLUENZA VACCINE**

In February 2012, the FDA accepted the first quadrivalent live-attenuated influenza vaccine, which is expected to substitute the currently available trivalent live-attenuated influenza vaccine in the 2013–2014 flu season. The quadrivalent vaccine is composed of both lineages of the circulating influenza B viruses (the Victoria and Yamagata lineages).\textsuperscript{62} A current analysis estimated that such a vaccine is probable to further decrease influenza cases, associated hospitalizations and deaths contrasted with the current trivalent vaccine. Similar to the current trivalent live-attenuated vaccine, the quadrivalent vaccine is inhaled.\textsuperscript{62}

**VACCINATION POLICY IN HEALTH CARE WORKERS**

In 2013, the Centers for Medicare and Medicaid Services will need hospitals to account number of their health care workers vaccinated. These rates will be openly reported as a measure of hospital worth. This has fueled the constant argue on mandating influenza vaccination for health care workers. Studies have revealed that the most essential factors in rising influenza vaccination rates among health care workers are the requirement of vaccination and its accessibility as a state for employment. As an option, some institutions have applied a “shot-or-mask” strategy whereby a health care worker who choose not to be vaccinated because of medical or religious reasons would be inquired to wear a mask through all face-to-face encounters with patients.\textsuperscript{63}

**NEW ANTIVIRAL DRUGS**

The appearance of oseltamivir-resistant strains recently presents a great challenge as far as the public health is concerned regarding the potential for occurrence of drug-resistant influenza.\textsuperscript{59,60,64-66} A present Asian randomized clinical trial reported the effectiveness of a long-acting neuraminidase inhibitor, laninamivir octanoate, in the management of seasonal influenza.\textsuperscript{67} Various studies explained that a single inhalation of this drug is effective in treating seasonal influenza, as well as that caused by oseltamivir-resistant strains in adults. Laninamivir is now approved in Japan.\textsuperscript{68-72}

**PREVENTIVE MEASURES**

All health care professionals should closely monitor
the community outbreak and the appearance of drug-resistant strains and strongly counsel vaccination for all patients older than 6 months, since appropriate vaccination is the basis of influenza avoidance. While many have asked the effectiveness of influenza vaccination, a current meta-analysis showed a 59% mutual effectiveness of the trivalent inactivated vaccine in adults age 18 to 65 years in preventing virologically definite influenza and 83% mutual effectiveness of the live-attenuated influenza vaccine in children age 6 months to 7 years.³³ New approaches for vaccination reminders, for example text messaging also the traditional mail or telephone reminders, can advance vaccination fulfillment in today's highly mobile world that is more than ever associated. With the instructions learned from four pandemics in the previous century, rationalized recommendation for anticipation, and sufficient vaccine supply, we must be prepared to face the challenge of another flu season.

CONCLUSION
The outbreak of avian flu again reveals the need for developing countries to be prepared to face unpredicted shocks at all times. Though, the burden of disease they cause and their economic impact could be really decreased by the right use of vaccines, antiviral drugs and public health interventions. Intensifying influenza surveillance, growing pandemic preparedness plans, improving management of avian influenza, and rising reporting of annual influenza vaccination are the keystone of a safer world. With local resources and capacities in each country and international collaboration will help attain essential goals. Otherwise, developing and industrialized countries would face an extraordinary global health crisis.

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