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Swine Flu is Back Again: A Review

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Abstract: Flu viruses have mainly affected humans, birds and pigs worldwide. During the past 10 years these viruses are in limelight at a global level due to pandemic threats of Avian / Bird Flu and Swine Flu and their public health impacts, with added pandemic of swine flu virus recently. The current ongoing episodes of bird flu and swine flu are beyond the control, when and where or which country they start with nobody can predict. The continuous evolution and emergence of new strains indicate that the flu viruses are becoming more and more dangerous and this situation has posed a challenge to researchers to discover effective vaccines and therapeutics. Moreover, the role of pig as 'mixing bowl' for the virus to get reassorted has added to the complicated epidemiological scenario. The swine flu H1N1 reassorted subtype caused the first global pandemic in last 40 years, resulting in substantial illness, hospitalizations of millions of peoples and thousands of deaths throughout the world. A pace is there within these novel and emerging flu viruses and the scientific community, where the scientific community has to win the race so as to save the mankind. In this review, a brief overview on swine flu is presented highlighting the characteristics of the causative virus, the disease and its public health consequences, advances made in its diagnosis, vaccine and control, precautionary measures to be adapted in the wake of an outbreak.

Key words: Swine flu, human, animal, diagnosis, vaccine, prevention and control

INTRODUCTION

Flu viruses affect a variety of animal species including pigs, horses, marine mammals, birds and also have caused human pandemics killing millions of people worldwide (Dhama *et al*., 2005, 2008; Chen *et al*., 2012; Mancini *et al*., 2012; Stack *et al*., 2013). With the improvement in transport and globalization, introduction and emergence of new influenza types and subtypes occur (Starbuck *et al*., 2012). Therefore, World Health Organization (WHO) has declared the threat of pandemic influenza posing a significant public health problem all over the world (Patriarca and Cox, 1997; King *et al*., 2004; Centers for Disease Control and Prevention (CDC), 2009; WHO, 2009; Ali *et al*., 2012). During the past 10 years these have been in limelight at a global level due to pandemic threats of Avian/Bird Flu and Swine Flu. Bird flu virus has caused severe economic losses to poultry industry and particularly since 2003 the H5N1 subtype has affected more than 60 countries resulting in loss of more than 300 million birds and 365 human lives (out of 617 affected) (Nayak *et al*., 2010). Alarming situation appeared again in 2009 when the reassortant H1N1 Swine Flu virus also knocked the door, reaching a pandemic status within few days, killing thousands of humans (WHO, 2009). The current ongoing episodes of bird flu and Swine Flu are beyond the control, when, where and which country will be affected, nobody can predict. The

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continuous evolution and emergence of new strains indicates that the flu viruses are becoming more and more dangerous (Guan *et al*., 2012), posing challenge to researchers to discover effective vaccines and therapeutics (Verma *et al*., 2012). Recent studies have indicated that human deaths due to swine flu might be much more as the disease is under reported or not diagnosed in many instances. Apart from these, Human Flu virus (H1N1) also causes approximately 36,000 deaths and more than 200,000 cases every year responsible for loss of over $10 billion in United States. Presently, another novel reassorted swine flu subtype H3N2 has emerged and is causing the menace (Jin and Mossad, 2012). In this review a brief overview on swine flu is presented highlighting the characteristics of the virus, disease and its public health consequences, advances made in diagnosis, control vaccine and precautionary measures to be adapted in the wake of an outbreak.

ETIOLOGY

Influenza viruses are enveloped RNA viruses belonging to Orthomyxoviridae family. The influenza (flu) viruses are highly contagious, able to spread very fast and easily across continents. These viruses has the ability to continuously change, resulting in emergence of new viral strains by genetic shift, point mutations and other mechanisms, posing threats to the host species particularly, in birds and humans (Dhama *et al*., 2005; Pawaiya *et al*., 2009; Lambert and Fauci, 2010; Hao, 2011). Type A influenza viruses are divided into 17 H (haemagglutinin) and 10 N (Neuraminidase) subtypes which can give rise to many possible combinations (designated as H1N1, H1N2….H2N1, H2N2….H5N1, H5N2…. and so on) (Dhama *et al*., 2005; Tong *et al*., 2012). The haemagglutinin (HA) plays role in attachment of the virus to the surface of infected cells while the neuraminidase (NA) plays role in release of the progeny viruses from the infected cells therefore NA plays role in spread of the virus (Wang *et al*., 2009). The influenza viruses primarily affect birds, pigs, equines and humans and are of significant concern as they could cause epidemics and pandemics. Of major concern are the influenza/flu viruses affecting birds, pigs and humans. Birds have alpha 2,3 sialic acid receptors in lungs while humans have alpha 2,6 receptors but swine have both the receptors, therefore pigs can be infected with avian, human and swine influenza viruses thus acting as a 'mixing vessel' (Ito *et al*., 1998; Dhama *et al*., 2005).

How the virus keeps on changing? Influenza/flu viruses keep on changing continuously giving rise to emergence of new viral strains. Genetic shift, point mutations and other mechanisms altogether help evolve more and more lethal flu viruses, posing threats to the host species particularly the birds and human beings (Dhama *et al*., 2005; Pawaiya *et al*., 2009; Lambert and Fauci, 2010; Hao, 2011).

Genetic or antigenic shift (reassortment/genomic mixing): Due to their eight segmented genome influenza viruses are capable of rapid evolution during mixed infections with different flu viruses (human, avian, swine) -A completely new subtype or a novel strain gets evolved (Chen *et al*., 2012).

Point mutations or antigenic drift: Point mutations are accumulated during virus replication and causes gradual evolution or acquisition of new strains of the same subtype, especially in the HA and NA glycoprotein genes, this process allows virus to escape the immune system and cause epidemics.

These major antigenic changes in HA or NA, results in periodic pandemics.

Swine influenza virus (SIV): The classical swine flu virus (H1N1) was isolated for the first time in 1930 from a pig. 'Swine influenza' or 'Swine flu' is a respiratory disease of pigs, caused by the swine flu virus and affects swine population round the year (Pawaiya *et al*., 2009; Said *et al*., 2013). During colder weather and winter months disease outbreaks are commonly seen. Among pigs H1N1, H1N2, H3N2 and H3N1 influenza virus subtypes are frequently reported, they could also be infected with H4N6 and H9N2 subtypes. The swine flu viruses do not normally infect humans. However, as pigs could act as mixing vessel for influenza viruses, events of reassortment and mutation would results in emergence of a novel influenza virus capable of causing human pandemics. Such an event started in April 2009 with H1N1 swine flu virus subtype (Garten *et al*., 2009; Pawaiya *et al*., 2009; Mak *et al*., 2012). This novel H1N1 reassortant virus has acquired the competence of rapid human to human spread without affecting pigs and has resulted in pandemic among in humans in many countries worldwide (Garten *et al*., 2009). The recently emerged H3N2 is a new reassorted subtype also has resulted in deaths of some children in United States (18 deaths in 1 week in Pennsylvania) (Chen *et al*., 2012). The major reservoirs of H1N1 and H3N2 influenza viruses are the pigs, in which influenza viruses reassort and could give rise to human pandemics.

EPIDEMIOLOGY, PUBLIC HEALTH IMPORTANCE AND PANDEMIC POTENTIALS/THREAT

Influenza viruses have affected animals and humans worldwide from time to time in the form of severe disease outbreaks, epidemics and even pandemics, causing severe economic losses and even threats to mankind (Dhama *et al.*, 2005; Pawaiya *et al.*, 2009). Pregnant women are at higher risk so World Health Organization (WHO, 2009) recommended the use of swine influenza vaccine in pregnancy. Direct transmission of influenza viruses can occur from pigs to humans and from humans to pigs.

The 20th century Human Influenza Pandemics:

- **Spanish flu: (1918-1919):** H1N1, an estimated 50 million deaths
- **Asian flu (1957):** H2N2, 1-2 million deaths
- **Hong kong flu (1968-1969):** H3N2, 1-2 million deaths
- **Swine flu (2009- till date):** H1N1, H3N2, 18,000 deaths

Key facts:

- In humans H1N1, H1N2 and H3N2 subtypes circulate commonly among people around world
- Few influenza virus subtypes (H5N1, H7N2, H7N3, H7N7, H9N2 and H10N7) have jumped the species barrier from water fowl/ birds to humans (Musa *et al.*, 2009; Pawaiya *et al.*, 2009; Murcia *et al.*, 2012)
- H5N1 caused severe economic losses to poultry industry worldwide and zoonotic threat to mankind, starting from 2003 and still continuing (Sarkar *et al.*, 2012)
- Pigs are considered as donator of the virus relatively easily, can act as 'mixing vessel' or 'mixing bowl' for genetic reassortment and pandemic influenza viruses could originate from these intermediate hosts. Pigs can spread the flu viruses in an open pathway without any barrier (Chambers *et al.*, 1991; Schultz *et al.*, 1991; Ma *et al.*, 2008; Kuntz-Simon and Madec, 2009) which has been depicted in Fig. 1
- The H1N1 subtypes had two genes from flu viruses that normally circulate in pigs in North America, Europe and Asia along with avian and human influenza virus genes, thus it is a "quadruple reassortant" virus with acquisition of man to man transmission capability
- The avian influenza virus (AIV) has yet to acquire the ability of rapid spread from human to human, as has been observed for the swine flu virus (H1N1 subtype) causing pandemic
- H1N1 swine flu virus (H1N1 triple human/avian/swine reassortant virus) caused human pandemic recently, started (Garten *et al.*, 2009; Pawaiya *et al.*, 2009; Shinde *et al.*, 2009; Smith *et al.*, 2009; Levy *et al.*, 2013)
- In 2011, a swine-origin influenza A (H3N2) virus infection were identified in two children (5 years of age) with history of contact with pigs and both had received seasonal influenza vaccine in 2010 (which contained the pandemic H1N1 swine flu virus strain) in US
- Currently H3N2 virus, a novel reassortment from swine has also been reported in August, 2012, with confirmed human cases affecting, children primarily in US (154) (Skowronski *et al.*, 2012) and Ohio (79) with history of exposure to pigs

This is especially important in the context of the concept of "original antigenic sin" which postulates that if a person in his childhood gets exposed to an influenza virus for the first time, strongest immunity develops in the later years to come. As a result of this people born before 1957 may show the greatest natural immunity to the A/H1N1pdm pandemic virus circulating at present (Chowell *et al.*, 2011; Rifkin and Schaal, 2012).

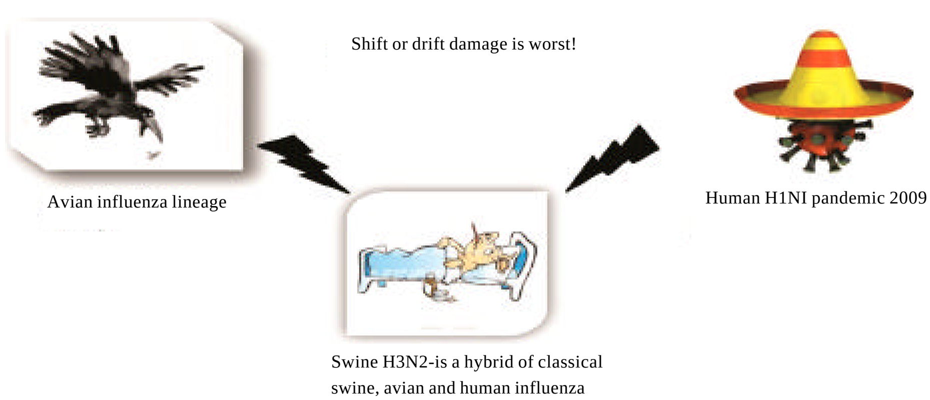

Fig. 1: Role of pigs in evolution of pandemic swine flu virus

SWINE FLU HUMAN PANDEMIC (NOVEL REASSORTANT H1N1 VIRUS) (2009-2012)

The H1N1 virus which causes swine flu, first appeared in Mexico in 2009 and rapidly spread around the world. Within 03 Months of the start of swine flu H1N1 human pandemic in April 2009 about 135 countries were affected with nearly one lakh of human cases and more than 500 deaths in USA alone (case fatality rate of nearly 0.5%) (Centers for Disease Control and Prevention (CDC), 2009; Pawaiya *et al*., 2009; WHO, 2009) (Table 1). Recent studies also indicate that the swine flu H1N1 pandemic would have killed many a thousands more since all the cases were not reported and many would have went undiagnosed and was estimated to be nearly 200,000 human casualties around the world. H3N2 which is new subtype has accounted for 145 cases.

High risk persons are those affected with chronic diseases of liver, lung, heart, kidney; and having diabetes, immunosuppression and neurological diseases.

Indian scenario: In India, swine flu has resulted in human casualties of 981 in 2009, 1,763 in 2010 and 75 in 2011. Swine flu is back in India on May 2012 resulting 129 cases with 12 deaths reported during this period of time. The major sufferer of this attack is Maharashtra with 69 cases and 6 deaths, followed by Rajasthan 28 cases and 5 deaths. One death has been reported from Andhra Pradesh as well. No deaths from Karnataka though there were affected cases. Recently in 2013, 456 cases along with 94 deaths have been reported so far in various states including, Rajasthan, Punjab, Haryana, Delhi, Himachal Pradesh.

Opportunities for emergence and spread of influenza viruses:

- A flu virus acquiring the lethal killing weapon of bird flu (H5N1) virus and rapid spread abilities of swine flu (H1N1) virus would evolve into a new/novel influenza virus and may result in as a probable pandemic threat to mankind. World population would be "immunologically naive" to this kind of a virus, permitting explosive spread of the disease that could cause serious socio-economic and public health consequences (Pawaiya *et al*., 2009)
- Overcrowding due to increasing human population of 7 billion (Mahima *et al*., 2012), increasing modern pig and poultry production ventures and proximity of humans and animals in many markets create potential for virus recombination and conditions conducive for the spread of the influenza virus and mass influenza outbreaks
- Rearing of pigs, birds (pet) and poultry together
- Increase in intercontinental travel within hours rather than months as in olden days and is in millions rather than hundreds

Table 1: World scenario of swine flu in the year 2009

Country	Human number affected
Mexico	159 died, 2498 affected
USA	7983 cases, 522 deaths
UK	Less than 5
Northern Ireland	14
Germany	3
France	1
New Zealand	14
Canada	6
Israel	2
Brazil	1
Malaysia	1

Based on of Centers for Disease Control and Prevention (CDC) (2009) and WHO (2009)

Animals, birds and humans living in close proximity places could create epicenters for influenza viruses. Ducks/chickens with pigs sharing ponds can very well contribute to the development of a reassortant virus. Pigs are known to be an intermediate host for the genesis of pandemic influenza viruses. Past pandemics reflect the role of birds in the generation of novel influenza virus reassortants.

DISEASE

In pigs: Swine influenza is a highly contagious and an economically important disease of pigs (Heinen, 2003; Pawaiya *et al*., 2009). Swine flu H1N1 is common among pigs as 25% of animals were found to carry antibodies by sero-surveillance. Among pigs the disease spreads by aerosols during close contact and also by contaminated objects/fomites moving between infected and uninfected pig sheds. If the virus is introduced for the first time into susceptible herds, then acute infections occur and may result in severe outbreaks. In the epidemic form, the virus quickly moves through the swine population followed by rapid recovery provided there are not complicating factors like secondary bacterial infections. In the endemic form, clinical signs may be less observed. Mortality rates are generally low in SIV infections, though morbidity can be up to 100%. Clinical signs occurs suddenly and the affected pigs exhibits signs like coughing, sneezing, nasal discharge, tachypnoea, dyspnea, pyrexia, anorexia and lethargy and some may occasionally show signs of fatal bronchopneumonia (Van Reeth, 2007; Simon-Grife *et al*., 2012), rarely pregnant sows may abort. Clinical signs usually persist for about seven days followed by quick and complete recovery unless complicated by secondary bacterial infections which can exacerbate the clinical manifestations (Easterday and Van Reeth, 1999;

Pawaiya *et al*., 2009). The disease causes high morbidity (as high as 100%) but low mortality if secondary bacterial infections are avoided.

There may be chance of sporadic disease with little or no any symptom, especially in herds where infections become a continuous problem or all the animals have been vaccinated.

In humans: Humans get infected by inhalation during close contact with infected pigs due to direct occupational exposure or in livestock exhibits housing pigs at fairs. Airborne human-to-human transmission can also occur. The affected individuals exhibits signs similar to that of human seasonal flu like fever, lethargy, loss of appetite, coughing, sneezing, sore throat, runny nose, difficulty in breathing, myalgia, headache, chills, fatigue vomiting and diarrhea (Pawaiya *et al*., 2009). In children neurological symptoms like seizures and changes in mental status like confusion or behavioral changes can also occur. Few such cases can be very severe and often fatal. The infected individuals could remain potentially contagious as long as they become symptomatic following onset of illness; children's could remain infective for longer periods (Iannelli, 2013). Young people below the age of 25 are more susceptible/affected (Simonsen *et al*., 2004; Pawaiya *et al*., 2009; Chowell *et al*., 2011; Rifkin and Schaal, 2012).

The H1N1 swine flu viruses are antigenically very different from human H1N1 (human influenza) viruses (Pawaiya *et al*., 2009). Therefore, human seasonal flu vaccines are not effective in cases of H1N1 Swine Flu viruses.

DIAGNOSIS

Presumptive diagnosis can be made based on clinical and pathological findings but confirmatory diagnosis requires detection of the particular influenza virus subtype in the affected host (birds, pigs or humans). Swine flu H1N1 virus can be detected by viral nucleic acid detection (Bertran *et al*., 2012; Read *et al*., 2012; Simon-Grife *et al*., 2012; Jackowska *et al*., 2013; Romanowska *et al*., 2013) or by serologic assays (Simon-Grife *et al*., 2012; Skowronski *et al*., 2012). Virus isolation can be performed in MDCK cell lines or primary swine kidney cell lines or in embryonated chicken eggs. Serological test like ELISA and molecular tools like RT-PCR, Real-time PCR are also used in the diagnosis of swine influenza (Yang *et al*., 2013). Respiratory specimen like nasal swabs, lung tissues should be collected within the first 4-5 days of illness when an infected person is most likely to be shedding virus (Alexander, 2008). Serum from acute and convalescent phase of infection can also be collected.

Bird flu and swine influenza viruses are zoonotic in nature and therefore the samples for diagnosis should be handled carefully to avoid transmission to humans. Precise and timely diagnosis needs appropriate samples to be sent to referral laboratories (choice and quality of specimens and the conditions for their transport and storage), having appropriate biosafety levels (BSL3/4) designated worldwide (Kumar and Henrickson, 2012). Respiratory samples viz., nasal swabs and lung tissues are to be collected within initial period of symptoms, preferably within first 5 days, as during this time only infected person most likely sheds virus (Alexander, 2008). Serum from acute and convalescent phase of infection can also be collected.

TREATMENT

Neuraminidase plays role in the release and spread of progeny viruses from infected cells and is the main target in the development of drugs against influenza viruses (Wang *et al*., 2009). Neuraminidase inhibitors like Oseltamivir (Tamiflu and Fluvir) and Zanamivir (Relenza) are widely used as anti-flu drugs in the treatment of swine flu cases in humans (Parmar *et al*., 2011; Hsu *et al*., 2012; Vijayan *et al*., 2012) but not in swine. Oseltamivir is the drug of choice. In pigs, usually supportive therapy and antibiotics treatment is carried out to control secondary bacterial infection.

PREVENTION AND CONTROL

Adequate prevention and control measures include strict biosecurity measures along with regular disease surveillance and monitoring programmes. Applying advanced diagnostics, stockpiling drugs like Tamiflu and development of novel vaccines utilizing recent tools and techniques and judicious vaccination strategies are of paramount importance in preventing the disease. These measures also limit epidemic potential and help avoid an imminent human pandemic (Pawaiya *et al*., 2009; Mak *et al*., 2012; Moukarram *et al*., 2012).

Adopt proper farm management practices along with good sanitation and hygienic measures like washing hands, following appropriate disinfection (sodium hypochlorite) and sanitary practices. Follow basic preventive measures, with strict vigil/ case identification and quick detection, isolation, quarantine, treatment of infected animals. Close contact with infected pigs should be avoided. People suffering from swine flu should take proper rest and must stay away from going to public places where numerous people gather. Safety measures such as wearing protective clothing, gloves, goggles, gown, rubber boots etc. must be taken care of during bird flu and swine flu disease outbreaks. Personal hygiene and

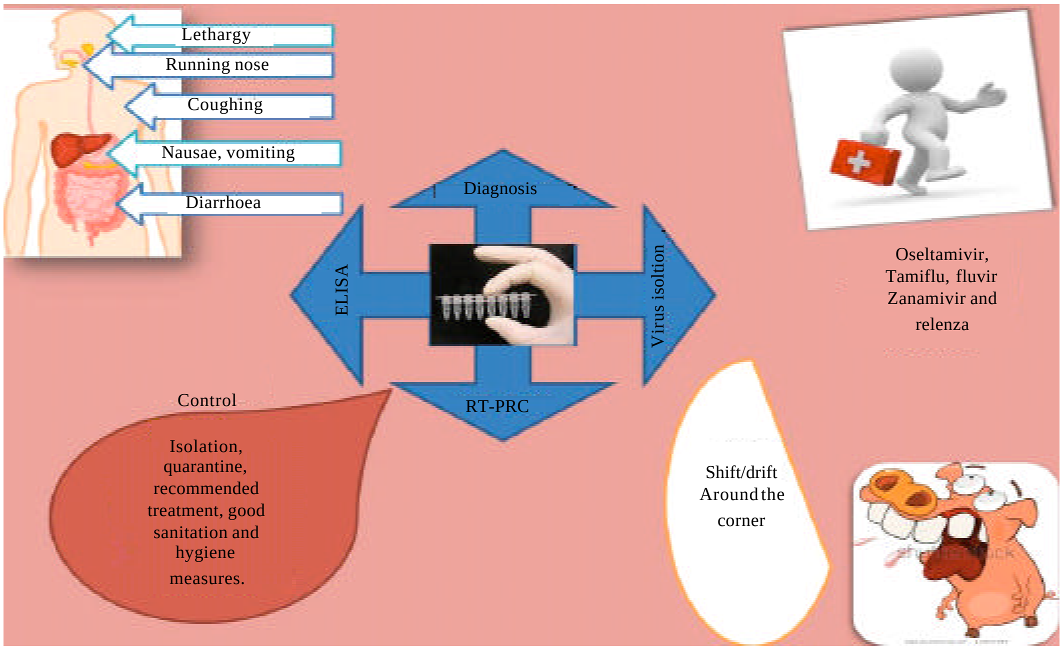

Fig. 2: Swine flu-Methods for diagnosing, treating, preventing and controlling it in human

biosafety measures should be adopted/upgraded like use of face mask, covering mouth and nostrils with tissue paper or handkerchief while sneezing or coughing and wash hands properly. Better wear surgical mask. Frequent hand washing helps reduce the chance of getting contamination from infected sources/fomites. Spread of infection can also be checked by avoiding touching of eyes, nose and mouth in the SIV contaminated environment. Drop the used tissue papers etc. in the dust-bin/trash during swine flu epidemics/pandemics. The virus is not transmitted by ingestion of pork so ingestion of properly handled and cooked pork is safe for humans.

Heightened vigilance and regular monitoring for identifying the influenza/flu cases is of paramount importance to prevent and control spread of bird flu and swine flu viruses and the flu pandemics. Regular and timely surveillance and tracking of influenza viruses at global level are the key factors for this purpose (Mak *et al*., 2012; Rebmann *et al*., 2012; Seetoh *et al*., 2012). International flights, train and surface transport should also come under strict surveillance. Wide public awareness on the prevention and control strategies as well as the zoonotic impact of bird flu and swine flu should be created using mass media (Pawaiya *et al*., 2009; Verma *et al*., 2012; Viveki *et al*., 2012). Along with it education and training programmes should be organized for para-veterinary professionals, animal and poultry farmers, animal transporters, etc (Ear, 2012). There should be some policy for filling the gaps in the knowledge of these influenza pandemic especially in developing countries (Kouassi *et al*., 2012; Cantey *et al*., 2013).

Methods involved in diagnosis, treatment, prevention and control of swine flu in human as discussed above is depicted schematically in Fig. 2.

Vaccines: For the prevention of swine influenza in pigs vaccines are available but are not proven to be 100% effective. The recombinant equine herpes virus-1 (EHV-1) encoding H1 of A(H1N1) pdm09 can protect the pigs against itself or any other influenza virus (Said *et al*., 2013). Only recently, for the current pandemic H1N1 strain the vaccine has been developed and approved by FDA and European medicines agency for use in US and UK, respectively. These include the chicken egg cultured swine flu viruses used as killed vaccine or as sub unit vaccine after digestion with detergent or cell culture vaccine (Vero or MDCK) and the cold adopted influenza virus. Vaccine for human influenza does not protect people against avian influenza infection and may lead to adverse effects following immunization with classical influenza vaccines (Wiwanitkit, 2009).

Two types of influenza vaccines are available namely:

- Trivalent Inactivated Influenza Vaccine (TIV), administered via injection
- Live Attenuated Influenza Vaccine (LAIV), administered via nasal spray

LAIV is not recommended for individuals under age 2 and over 49 year's age.

Effective vaccines for protecting birds as well as humans against the novel reassortant H1N1 and H5N1 subtype virus are the need of hour.

CONCLUSION

Disease outbreaks of bird flu and the recent swine flu pandemic and their public health impacts with probable potential of a deadly human pandemic have created an alarming situation worldwide. Fortunately, swine flu did not acquire the lethality like that of bird flu virus having nearly 60% case fatality rates, in which case a deadly pandemic would begin threatening human survivability. Continuous global efforts are on the way so as to gain better understanding about the virus, focusing on its pathogenesis, genetic versatility, zoonosis, pandemic potential, treatment and control. Prevention and control strategies focus on strict biosecurity, adequate disease surveillance, timely diagnosis, appropriate culling measures and judicious vaccination measures along with adequate public health and biosafety measures. Since the appearance of this disease is unpredictable, these responses must be prompt, well planned and complete. SIVs do not normally infect humans and had been only responsible for sporadic zoonotic infections. However, the current novel influenza A (H1N1) swine flu virus has caused pandemic situation in several countries due to gene swapping amongst between avian, swine and human viruses. Swine flu viruses does not cause any illness in pigs but change constantly like the other Type A influenza viruses which poses difficulty in developing a permanent, long-lasting and effective vaccine. Though the recent/current swine flu pandemic is looking moderately severe at present but if the virus acquires the deadly lethality like that of bird flu virus then situation would be worst for the survivability of mankind. Possible pandemic threat posed by the highly pathogenic H5N1 bird flu virus and the H1N1 swine flu subtype or with an emerging new subtype, if happens could be catastrophic for humans considering its past lethality rate.

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