Research & Reviews: Journal of Hospital and Clinical Pharmacy

Newer Approaches in the Treatment of Swine Flu

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Review Article

Received date: 26/05/2018
Accepted date: 28/06/2018
Published date: 03/07/2018

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Keywords: Swine flu, H1N1, Chronic obstructive pulmonary disorder, WHO, virulence

ABSTRACT

This review article focuses on different aspects such as the history, epidemiology, treatments, and preventive measures of swine flu. This is caused due to H1N1 virus which contains eight strands, one of them is derived from the strains of human flu and 2 are from the strains of avian and the other 5 strands are derived from swine strains. It was

Termed as H1N1 flu, which has two main antigens H1 is hemagglutin type 1 and N1 is neuraminidase type 1. A novel drug delivery system is also researched in order to offer the most efficient treatment for swine influenza. This system helps to overcome drawbacks like severe toxicity and hypersensitivity hence is of immense significance in treating swine flu.

INTRODUCTION

Swine flu has been one of the emerging pandemic disease that is caused by different variants of H1N1 influenza viruses. This virus was firstly discovered in America in 2009 and the virus most extensively studied nowadays. Swine flu is also termed as pig influenza, swine influenza, hog flu and pig flu. Swine influenza virus [SIV] or S-OIV [swine-origin influenza virus] is one strain of the influenza family of viruses that is prevalent in pigs. Till 2009, the known SIV strains comprised of influenza C and the subtypes of influenza A which are known as H1N1, H1N2, H3N1, H3N2 and H2N3. Swine flu viruses have been reported to spread from person-to-person, but this transmission was restricted in the past and not constant beyond three people.

HISTORY

In the year 2009, the cases of influenza swine fever [H1N1] in humans were initiated from California and Texas then reported in other states such as Mexico. Later in 2009, it was labelled as "swine flu", this flu was caused by 2009's new strain of swine-origin A/H1N1 pandemic virus [pdmH1N1] just as it was earlier called as "avian flu". This flu caused by the current Asian-linage HPAI [High Pathogenic Avian Influenza] H5N1 strain that is still widespread in many wild bird species in several states. Swine flu was first proposed to be a disease referred to human influenza during the 1918 flu pandemic, when pigs fell ill at the same time as man. In 1930 the first identification of an influenza virus as a cause of disease in pigs prevailed after a decade. [1] For the following 60 years, swine influenza strains were almost exclusively considered as H1N1. During the period of 1997-2002, new strains of three different subtypes and five different genotypes of H1N1 emerged as the origins of influenza among the pigs in North America. New H3N2 strains were developed in the year 1997 to 1998. These strains, which include genes derived by swapping of gene segments of human, swine and avian viruses, known as re-assortment, have become a main cause of swine influenza in North America. Re-assortment between H1N1 and H3N2 strains lead to the emergence of H1N2. In Canada, a strain of H4N6 crossed the species obstacle from birds to pigs, but was limited on a single farm by 1999 [2]. The phylogenetic origin of the flu virus was initiated the 2009 pandemics can be sketched before 1918. Around 1918, the familial virus of avian origin, crossed the species boundaries and diseased humans as human H1N1.The same phenomenon was happened shortly in America, where the human virus was infecting pigs. This leads to the advent of H1N1 swine strain, and advance into the classic swine flu. The new human H1N1 flu strain of bird origin, was kept conveying, among human populations until around 1957, when there was a co-infection amongst this strain and the bird H1N1 in humans. There was a re-assortment event leading to the progress of a new

strain [H2N2]. New events of re-assortment were not testified until 1968, when the avian strain H1N1 infected humans again. During that time, the virus met the strain H2N2, and the re-assortment originated the strain H3N2. This newly found strain has remained as a stable flu strain till date. The crucial moment of the 2009 outbreak was found in between 1990 and 1993. There was a triple re-assortment occurrence in a pig host. The reassortment in North American H1N1 swine virus the human H3N2 virus and avian H1N1 produced the swine H1N2 strain. The last step in S-OIV history occurred in 2009 when the virus H1N2 co-infected a human host simultaneously as the euro Asiatic H1N1 swine strain. This resulted in the emergence of a new human H1N1 strain which triggered the 2009 pandemic.

In case of swine flu there are major changes observed in the hemagglutin structure. In 1946 the new strain of swine flu hemagglutin showed change was identified as A1 or A prime. In 1957, Asia witnessed another change in hemagglutin where the strain was termed as A2. Another major alteration in hemagglutin was seen in the year 1968 at Hong Kong, this time the strain was termed as A2 subtype for antigenic drift. The neuraminidase is also capable to undergo independent antigenic variation. This extended the role of WHO in 1971 to come up with a new system of classification that considered the nature of both the surface antigens neuraminidase and hemagglutin. The hemagglutin of the type A0, A1, A2 [Asian] and A2 subtype [Hong Kong] were renamed as H0, H1, H2 and H3 respectively. This classification altered by grouping Hsw, H0 and H1 under the denotation H1. The neuraminidase were of two subtypes N1 which was seen in A0 and A1 strains and N2 which was found out in A2 [Asian] and A2 subtype [Hong Kong]. The complete denotation of the strains includes its type, place of origin, serial number, year of isolation and antigenic subtypes of surface antigens of hemagglutin and neuraminidase. In case of strain A/Hong Kong/ 1/68 [H3N2v] v stands for the variant.

The Structure of Virus

The nucleocapsid is a bilayer structure in which the composition of the inner membrane is proteins and the outer layer is lipids. From this double layered envelope surrounding the nucleocapsid, there are projections emerging which are of two types of hemagglutinins and neuraminidase. The virus is roughly spherical or sometimes filamentous forms with size ranges. The size of the virus ranges from the 80 to 120 nm. Nucleoproteins [NP] coat the centrally located viral RNA and their segments are associated with a trimetric polymerase complex which is collectively referred as a viral ribonucleoprotein [vRNP] complex where the matrix protein [M1] forms the core **Figure 1**.

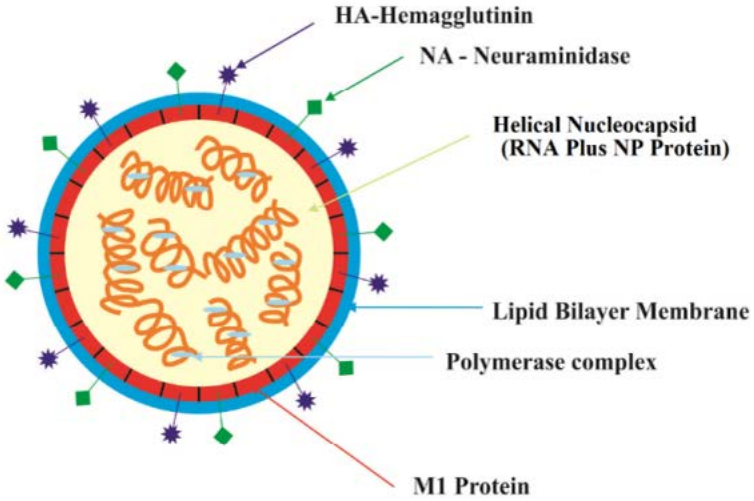

Figure 1. Structure of H_1N_1 virus.

Antigens

The antigens of the influenza virus are of two types: surface antigens and internal antigens. The internal antigen is a type of ribonucleoprotein, also it is known as RNP antigen. When the virus containing fluid is centrifuged and the supernatant observes indicate RNP antigen. Because of RNP antigen, which exists in free form in the tissues? The RNP antigen is therefore known as S-antigen [soluble antigen] and is specific and different when change in influenza viruses observed. All the three types A, B and C of RNP antigen are different, but in all strains of any one type possess the same antigen. The RNP antigen is very static and does not show any antigenic variation, but M protein antigen showed type specific and different nature of influenza types A, B and C. This type of antigen is host specific and dependent on the species of the virus undergo replication. The surface antigen or V antigen has two proteins hemagglutin and neuraminidase. Hemagglutin is a type of glycoprotein which comprises of two polypeptides HA1 and HA2 and enables the virus to adsorb on the mucoprotein receptor cells. These receptors are present in the epithelial cells of the respiratory tract and on red cells. Hemagglutin is strain specific antigen and tends to show great variation. It has eighteen different types denoted from H1 to H18 but only four types are responsible for causing influenza virus associated

diseases in humans. Neuraminidase is a glycoprotein enzyme which is responsible for destroying cell receptors by hydrolytic cleavage. It is also a strain specific antigen and shows different types N1 to N9.

The influenza virus has ability to undergo antigenic variation in influenza type A virus and rarely seen in influenza type B virus. The influenza type C does not sustain the power to show antigenic variation. The internal S antigen and M antigen are stable, but hemagglutin and neuraminidase are capable to show the antigenic variations. The antigenic variation is of two types: antigenic drift or antigenic shift [3]. The gradual change in antigenic structure is determined at regular intervals is known as antigenic drift. This type of shift is due to mutation and selection which is influenced by the type of antibodies present on the host cells. The periodical epidemics of influenza occur due to antigenic drift [4]. The antigenic shift is major abrupt, discontinuous variation in antigenic structure. Such type of shift involves both hemagglutin and neuraminidase and this antigenic shift spreads easily causing epidemics.

Inactivation of Virus

The virus can be inactivated by heating at 50 ℃ for 30 min but virus remains viable at a temperature of 0 to 40 ℃ for a time span of 1 week. The viruses are preserved by storing at -70 ℃ or by using the freeze drying technique. The virus can withstand slow drying and thus it can remain viable on fomites such as blankets for more or less 2 weeks. Several agents like formaldehyde, ether, phenol, salts of heavy metals may be utilized to destroy the virus. Iodine has proved to be the most effective in destroying the virus.

Epidemiology

The different viruses H_2N_2, H_3N_2, H_5N_1, H_1N_1 causing swine flu [5], morbidity rates, and time of occurrence has been explained in **Table 1.**The global scenario for the swine flu cases as of 2009 is stated below in **Table 2** [6].

Table 1. Representative data on the virus, with respect to its occurrence and morbidity.

Year	Virus	Number of deaths
1957	H_2N_2-Asian flu	1.5–2.5 million
1968	H_3N_2-Hong Kong flu	700000
2004-2009	H_5N_1	262
2012	H_1N_1	405
2014	H_1N_1	218
2015	H_1N_1	More than 2000 deaths

Symptoms and Diagnosis

The most common symptoms of swine flu include cough, sore throat, chills, pneumonia, URI [upper respiratory infection], fatigue and body ache, running nose, fever, vomiting and diarrhoea [7]. These symptoms are very common in other conditions too, and hence sophisticated diagnosis should be required for swine flu.

On an initial stage the diagnosis includes regular chest X-ray and blood test to confirm viral infections, whereas the latter includes the collection of nasopharyngeal samples and checking for influenza type A and B. This can differentiate between A and B type of influenza if the test is positive for type A influenza then the virus is likely to be associated with swine flu. However, this test may not be completely accurate; hence a specific polymerase chain reaction based diagnostic test is carried out in civil hospitals to confirm swine flu. Antigen detection tests as well as neuraminidase assay are also used as one of the major diagnostic methods [8].

Table 2. Representative data of the regions being affected by swine flu, cases and deaths.

Regions	Cases	Death
Africa	8352	42
America	137147	3020
Eastern Mediterranean	12008	74
Europe	Over 56000	At least 176
South East Asia	33594	413
Western Pacific	96197	383
India	10036	308

Risk Factors and Complications

Swine farmers [farmers rearing pigs] are at risk since they are more exposed to the pigs during rearing them. Hence the transmission from the infected pig to the farmers is extremely possible. Veterinarians are also at risk while treating the infected

pigs. However, recent phylogenetic studies suggest that humans infect pigs with human lineage influenza A viruses much more than swine lineage viruses infect humans. People visiting crowded places or people gathered in huge numbers show a higher tendency to get infected since swine flu is a contagious disease. Geriatrics and pediatrics are prone to develop the symptoms of swine flu much faster because of weaker immunity response. It is also analyzed and concluded that the age group of 29-40 years have the highest probability of developing swine flu. The different complications which may attach to the natural complications of swine flu are pneumonia, respiratory failure and chronic conditions like asthma and COPD [9].

TRANSMISSION

The H_1N_1 virus is contagious and spreads easily from person to person via touch, inhalation, blood and sexual contact. Transfusion of blood from an infected person to a healthy person will make the transport of the virus to the healthy person's blood [10]. Adsorption of the viruses on the surfaces through the nose or mouth can easily infect any person. H_3N_2V is less contagious as compared to H_1N_1 virus [11]. H_3N_2V requires a direct transmission from pig to man. Hence people working on pig farms are more prone to get infected with this virus as well as individuals consuming pork meat which are infected. Moreover, high chances of the health care professionals are infected with the virus since they are in touch with the patients of swine influenza. The transmission rate of swine flu increases in winters and monsoon because H_1N_1 virus gets denatured at high temperature which destroys its virulence. Therefore casualty of swine flu is noted mostly in the winter and rainy season [12].

Conventional Treatment Approaches

Chinese system of medicine is also equally effective in treating swine flu. It uses herbs like *Fructus Forsythia Suspensa, Flos Lonicera Japonicae, Radix Isatidis seu Baphicacanthi, Folium Isatidis seu Baphicacanthi, Herba Andrographis Paniculatae, Rizhoma Dryopteris crassirhizoma, Radix Ilicis Pubescends, Rhizoma Paridis Polyphyllae, Herba cum Radix Patriniae, Radix ET Rhizoma Polygoni Cuspidatti, Herba cum Radice Violae Yedoensis, Radix Glycyrrhizae Uralensis and Herba Mentha Haplocalyces* [13]. The **Table 3** shows the list of herbs and their applications to handle swine flu influenza.

Table 3. Different herbs and its activity used for treatment of swine flu in the Chinese system.

Herb name	Use
Gypsum and Folium Lophatherum	Relieve fever
Rhizoma Phragmites and Fructus Arctii Lappae	Treat sore throat
Radix Bupleurum and Radix Scutellariae Baicalenses	Enlargement of lymph nodes
Radix Puerariae and Radix Bupleurum	Treat chills and shivering
Fructus Gardenia Jasminoides and Radix Scutellariae Baicalenses	Treat harsh cough

Homeopathy is also used at times in treating swine flu. The various herbs and their remedial actions have been listed in **Table 4** [14,15].

Unani (Perso-Arabic) system of medicine also causes its own approaches for handling swine flu. Includes the steam inhalation of Arq Ajeeb also known as kulzoom by addition of 4 to 8 drops in fresh water and the remedy is taken 4 times a day. Kaffori balm is rubbed gently on nose, chest 5 times a day. Joshina syrup is to be taken with half cup of water empty stomach morning and evening. Sharbat nazal two tea spoon+sharbat bansfha two tea spoons+hot water should be taken 2 times a day. Habbe giloey 2 tablets+habbe bukhar 1 tablet should be taken as advised by the physician.

Table 4. Different herbs and its activity used for treatment of swine flu using Homeopathy.

Herb name	Use
Gelesmium	Relive body aches
Aconite	Reduce cough, more effective in children
Baptisia	Treat diarrhea
Eupatorium perfoliatum	Treat early flu stages
Ipecac	Treat the associated gastric symptoms
Allium cepa	Reduce severity of flu
Rhus toxicodendron	Relive aching of bones, sneezing, coughing

Ayurveda [Indian origin] has a remedy which helps when used to the allopathic medicine. Tea can be consumed two to three times a day. The formula for the tea is explained in **Figure 2** [16].

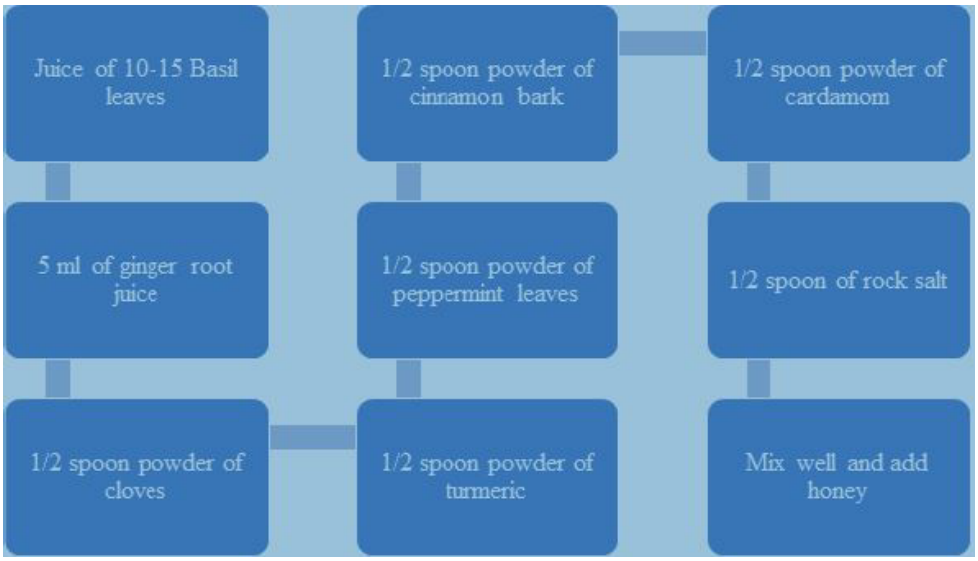

Figure 2. Ayurvedic remedy for treatment of swine flu.

An Inference Drawn from Conventional Treatment Approaches

The modern treatment approaches focus on symptomatic treatment to get temporary relief from the symptoms, but a complete cure of swine flu is compromised with this approach. Hence, to assist the need of the hour for complete cure as a desirable outcome these conventional treatment approaches have been focused on. The treatment approach using conventional system is uniquely tailored based on individual constitution of the patient. Some of the synthetic antivirals used to treat swine flu also come from plants. Tamiflu is an example such antiviral, originates from the herb *Illicium verum*. Also, using such kind of herbal treatment approaches mostly never develop resistance compared to synthetic antiviral agents in modern treatment therapy. The herbal treatment usually uses the single drug to treat all the symptoms, whereas in modern system multidrug is used to relieve the patient from the symptoms. The advantage of a single drug is that the exact effect of the drug may be known also there no chances of drug-drug interaction.

The most common disadvantage of such conventional approaches is that the cultivation of the herbs is difficult to require a larger number of skilled labour as well as land. The quality of the drugs available will be compromised if appropriate climatic conditions, soil requirements and the time of sample collection is varied. The regulation of herbal drugs is not that stringent hence there is a high probability that drugs used are of inferior quality. Since swine flu progresses in a very short span of time the usage of conventional approach may lead to worsening of the conditions as herbal treatment works at a slower rate. The wild herbs are used, sometimes associated risk of poisonous due to other unnecessary impurities. Also, when herbs are used along with synthetic drugs, there are high chances of interaction which leads to undesirable effects during treatment.

Advance Treatment Approaches Involving the use of Antivirals

Antiviral drugs like Oseltamivir [Tamiflu], zanamivir [Relenza], rimantadine and amantadine are used in treating swine flu since it is a viral infection. The structure of these drugs is listed in **Figure 3** [17].

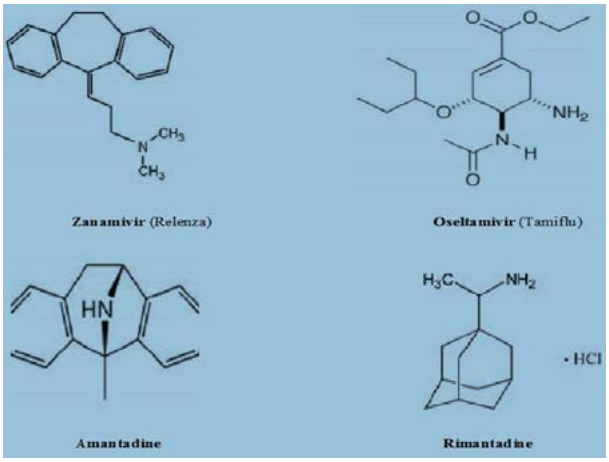

Figure 3. Chemical structures of antivirals.

Rimantadine and amantadine are not recently used because of their side effects and development of resistance in swine flu. These drugs are M_2 channel inhibitors, but showed the effects like shortness of breath, chest tightness, wheezing and difficulty to breathe. Rare side effects include nausea, abdominal pain, and hearing loss, development of rashes, unusual tiredness and drowsiness. The overdoses of drugs leads to the symptoms like fainting, anxiety, dry mouth, dizziness, rapid pulse, irritability and trouble while sleeping **Figure 4**.

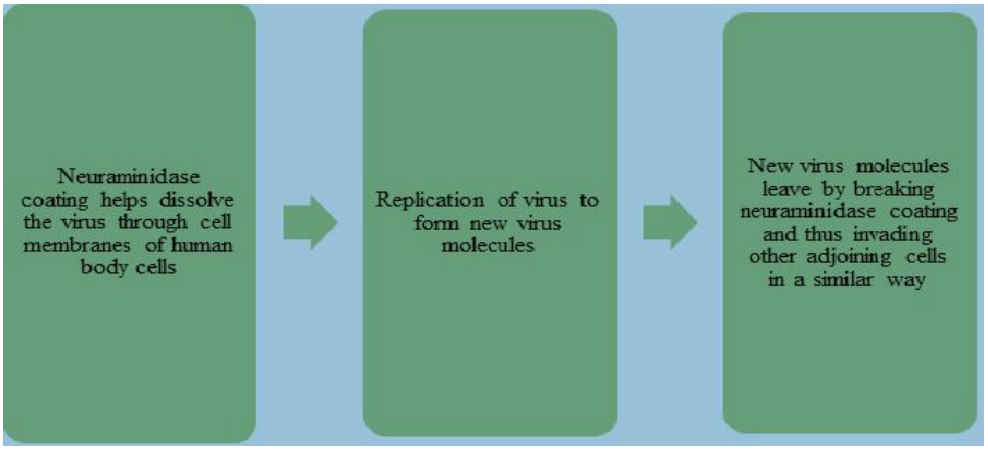

Figure 4. Mechanism of Tamiflu and Relenza.

Tamiflu binds to the neuraminidase layer of the virus by inhibiting its ability to escape from the infected cell. Hence tamiflu flu works effectively only when it is taken at an early stage of the disease since it only inhibits and not destroys the virus [18,19]. Vomiting and nausea are common side effects of tamiflu [20]. It is used for adults and children above the age of 1 year. It is contraindicated in patients with severe skin allergies, Steve-Johnsons syndrome, toxic epidermal necrolysis, and erythema multiform. The other opposing consequences occurring in<0.99% of infected subjects receiving Tamiflu dosage to undergo the treatment of swine flu include unstable angina, ischemia, pseudomembranous colitis, humours fracture, pneumonia, pyrexia, and peritonsillar abscess.

Dose of medication: 75 mg twice for 5 days [for age group above 13 years]; Dose for prevention: 1 dose once for 10 days [for age group above 13 years]. It is available in the forms of oral suspensions and capsules. Relenza is neuraminidase inhibitors which binds to the neuraminidase and prevents the working of neuraminidase Common side effects include the development of rashes on the skin, throat tightness and difficulty in breathing. Some rare side effects include swelling of face and severe allergic skin reactions. Patients with underlying airway diseases are not recommended for treatment or prophylaxis of influenza [e.g. asthma and COPD] due to serious bronchospasm [21].

Thus, if a decision is made to use the drug in such patients, respiratory function should be monitored carefully an appropriate supportive care should be available which include β-adrenergic bronchodilators.

Dosage for treatment: 10 mg twice for 10 days [for age group above 7 years]. It is available in the forms of nebulizer as well as an intravenous infusion.

Line of Treatment for Antivirals as Per WHO

Irrespective of more than 5 days of antiviral treatment being effective, monitoring of shedding and replication of the virus, and dosing of antiviral drug, susceptibility test is demanded for the possible detection of the active virus. Among the two antivirals oseltamivir and zanamivir, the most preferred drug is zanamivir as oseltamivir has been reported for demonstrating resistance as compared to zanamivir in most of the cases. Patients facing chronic and progressive degradation [mechanically ventilated patients] in their clinical condition and are unable to consume medications orally, nasogastric tube can be put to use wherein the drug passes through the nasal cavity. It directly comes in contact with the gastric mucous membrane, thus enhancing better absorption of the drug [22].

Other Treatment Considerations as per WHO

Timing of commencement of treatment: The treatment must commence at the earliest even if the initial laboratory diagnosis is negative for swine flu since there might be a probability that a patient shows the progression of the disease a little later. Starting the empiric treatment at the earliest is suggested.

Dosing technique: High dose of Tamiflu for increased duration of treatment are preferred. However, there is no clinical evidence that this is the most efficient treatment option available. One hundred and fifty mg doses twice a day is administered in cases of critically ill patients. When the patient has complications like renal impairment the doses of tamiflu may be modified

as there is a risk of higher systemic exposure of tamiflu. After 5 days or more of antiviral treatment, the disease still remains progressive than the virus replication and virus shedding needs to be monitored. There is also a need of antiviral drug susceptibility test in such incidences. The antivirals employed in treatment should be administered without a break until there is satisfactory clinical improvement.

Drug resistance: If the patient is found to be resistant to the antiviral agent, used for the treatment should be immediately replaced with another anti-viral drug. Relenza is preferred in such cases. Short-interfering RNAs [siRNAs] are the modern class of potential antiviral therapeutics to be advanced. Current reports using siRNAs in mice propose that they hold great potential for prevention and treatment of influenza A virus infection [23].

Advanced Treatment Approaches

Vaccines are also used in the treatment and prevention of swine flu. There are various types of vaccines, which are used to provide immunization.

Live attenuated vaccines contain live microbe which has been weakened hence they are not capable to cause the disease. They provide lifelong immunity since they have a very strong cellular and antibody response [24]. Hence it requires 1 or 2 doses to develop immunity. The microbe used has a tendency to mutate, which might lead to microbe virulent hence it's a severe drawback to use live attenuated vaccines. This type of vaccines cannot be given to people with a weak immune system. The other limitation of this type of vaccine is that it needs to be continuously refrigerated while shipping and storage for a long time which is difficult.

Inactivated vaccines contain dead microbes in vaccines. The microbes are killed by exposing them to chemicals, radiation or heat. This type of vaccine is a safer approach to use because the microbes cannot mutate as they are dead. Hence there are no chances to regain its virulence. Most of the inactivated vaccines do not require refrigeration since they are kept and delivered in the lyophilized [desiccated] form [25]. This vaccine type has a weaker response to immunity because of the large number of doses are required to develop a stronger immune response. It may not always be feasible to visit the place to take regular doses of vaccine. The efficacy of inactivated influenza vaccine depends on the age, similarity between the viruses in circulation and the viruses in vaccines and the immune-competence of the vaccine recipient [26]. Subunit vaccines include only the antigen, which is responsible to provide the best immune response. Since this type of vaccine has only the antigen and not the molecules, the possibilities

of antagonistic reactions are happened least. A subunit vaccine can receive 1 to 20 or more antigens. The process to identify and isolate specific antigen that provide the immune response is a very time consuming phenomenon. Recombinants DNA technology may be used to manufacture the antigen to such vaccines are termed as recombinant subunit vaccines.

Toxoid vaccine is of significance when the toxins are being generated by the causative agent. The toxins can be deactivated, but treating it with formalin [formaldehyde+water] such deactivated toxins are termed as taxis. The body learns how to defend natural toxins by locking on the toxin and blocking its action. Conjugate vaccine is used when the disease causing agent has an outer coating of polysaccharides since it can easily mask its antigens. The toxoids or antigens are linked in such a way that the body's immune system can recognize its antigen [27]. The vaccine protecting against influenza type B is of this type. DNA vaccines may be used when the complete genetic composition of the virulence imparting organism is known. It helps induce a strong immune response. It is easy to prepare, less expensive not causing the disease [28]. The mechanism of action of DNA vaccine acts is represented below in **Figure 5**.

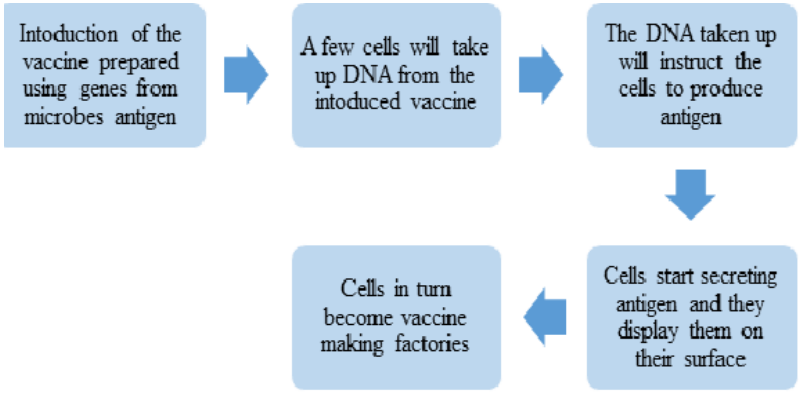

Figure 5. Action of DNA vaccine.

Naked DNA vaccines are used to provide immunity against influenza virus. Such vaccines contain DNA as their constituent and are administered using a needle and syringe or high pressure gas which helps the particles to enter the targeted cells easily. Sometimes DNA of the antigen is coupled with other components that help to enhance its permeability and immunizing ability.

Recombinant vector vaccines are correlative to the DNA vaccines, but they utilize attenuated virus to access the DNA into the body. Vector is the bacteria or virus which is being used as a carrier. They closely resemble to a natural infection, hence produce a very strong immune response. For HIV infection the recombinant vector technique using bacteria as well as the virus has been studied since the structure of swine flu virus is similar to HIV. This approach may work in providing immunization against swine flu.

Some of the marketed vaccines available for swine flu are included in the **Table 5** [29,30].

Table 5. Marketed vaccine available for swine flu treatment.

Sr.Name	Brand Name	Manufacturer	Forms Available
1	Agripal	Chiron Panacea [Panacea Boitech Ltd]	Injection
2	Fiurax	Glaxo Smithkline Pharmaceuiticals Ltd	Injection
3	Influgen	Lupin Laboratories Ltd	Injection
4	Influvak	Solvay Pharma India pvt Ltd	Injection
5	NasoVak	Serum Institute of India Ltd	Injection

One of the vaccines used for swine flu treatment was developed by GSK [Glaxo Smith Kline]. The viruses used for vaccine manufacturing are grown in eggs. The vaccines have two components antigen and adjuvant which are mixed before administration in an inactivated form [31].

The composition and list of vaccines are shown in **Figures 6** and **7** [32].

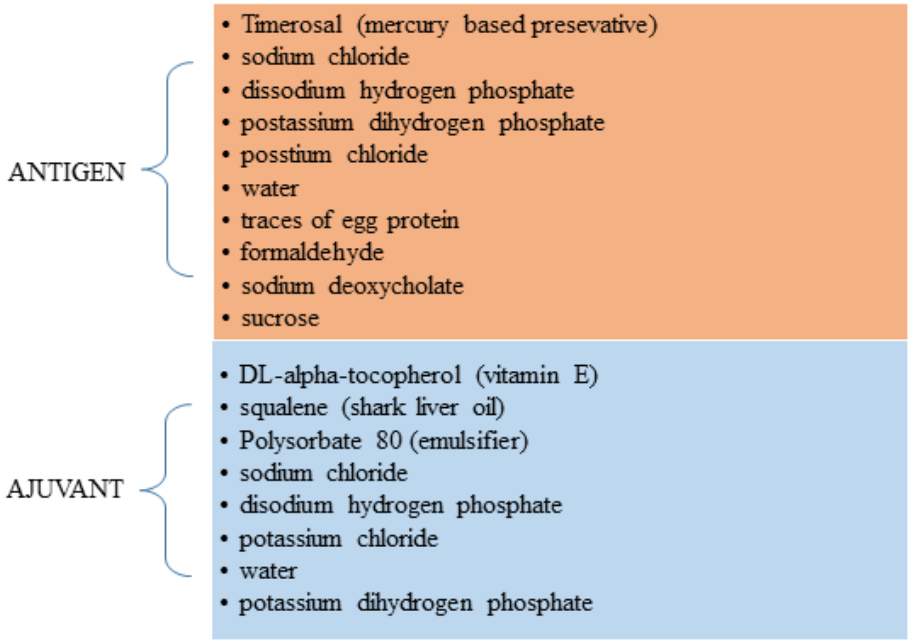

Figure 6. Composition of vaccine.

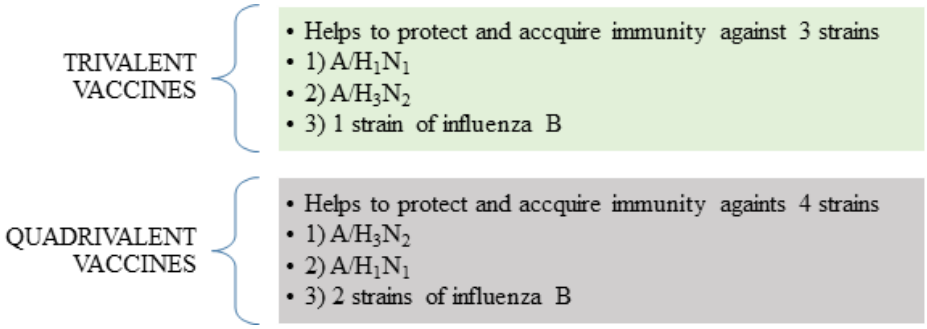

Figure 7. Types of vaccines.

An Inference Drawn from Advance Treatment Approaches

Using advance treatment approaches the swine flu pandemic can be managed better. There are very stringent norms for the regulation of the quality of drugs used. So there are less chances of drug being of inferior quality. Hence the therapeutic action of the drug is not compromised and its efficacy is always maintained. The therapeutic action of the drugs is faster in the advance approaches as compared to the conventional approaches. There is only symptomatic treatment of the disease in the advanced approach. The drawbacks of using such kind of approach include major side effects like hypersensitivity, nausea, headache, swelling of the face, etc. The safety profile of the drugs used in advance treatment approaches is not completely known so there are chances of developing toxicity in some cases which may prove to be fatal. There is a probability of undesirable drug-drug interaction when two or more drugs are used in combination. However, sometimes drug-drug interaction might be desirable when the drugs used in combination to provide better therapeutic action as compared to when drugs are used individually. Since some of the synthetic antivirals like Tamiflu come from herbs, there is a problem of cultivation, climatic requirements and need of skilled labor for the procurement of the herb. In some of the cases using the advance approaches and conventional approaches together may work well and provide quick relief from the disease. However, still there is a need for a better treatment approach which is more efficacious than these approaches.

Novel drug delivery approach is one such treatment strategy wherein the drug efficacy is improved by using the techniques of polymer science, molecular biology, pharmaceutics and bio-conjugate chemistry. This type of approach may help to overcome the problems associated with toxicity, stability and bio-recognition. It may also help to avoid side effects, increase the bioavailability of the drug and help in modifying the release pattern of the drug. It also helps to enhance the permeability and penetration of the drug in turn increasing its ability to target wider range of tissues. They help to target a precise location where in the drug reaches intact only to the infected cells. Hence the development and improvement in these approaches very interested in treating swine flu.

Novel Drug Delivery Treatment Approaches to Vaccines

Colloidal drug delivery systems for vaccines is of immense importance since using a conventional vaccine delivery system has severe drawbacks which include problems associated with toxicity, hypersensitivity reactions, etc.

Colloidal drug delivery systems are considered to be more safe and effective. It can be used to provide immunization by oral and transmucosal routes. This type of drug delivery system has better immune recognition. It uses particles in the range of 1 to 1000 micrometers [33]. The various particles used in this approach are stated in **Figure 8**.

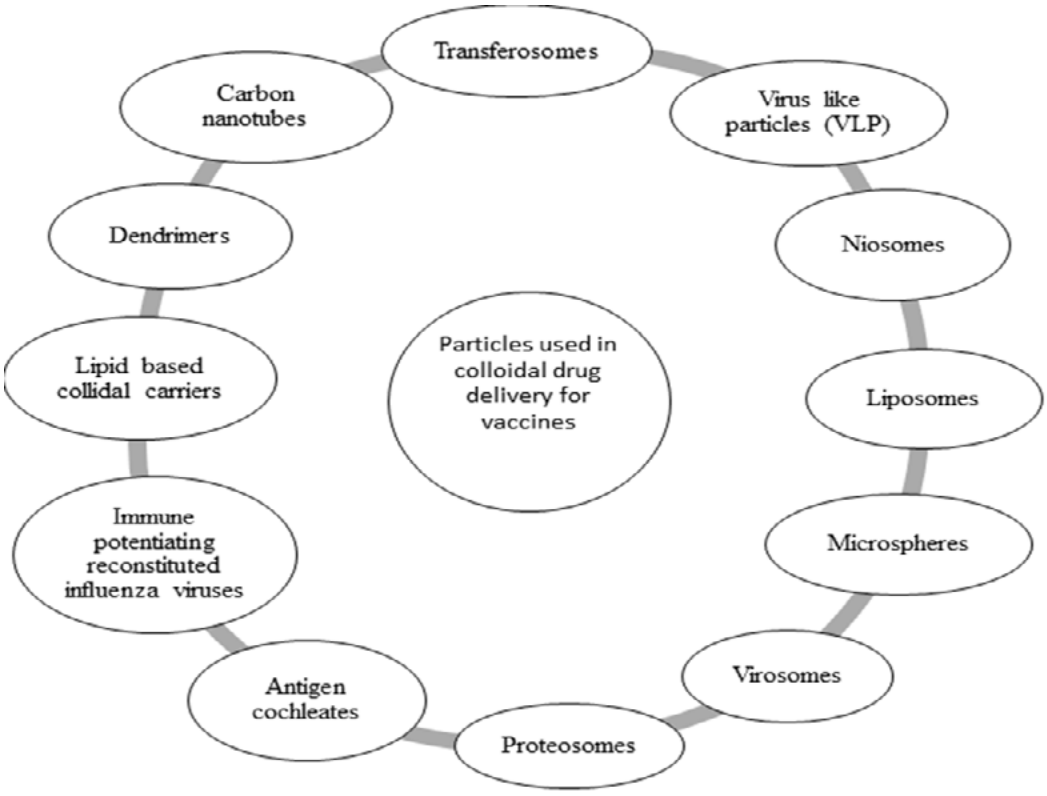

Figure 8. Carriers used in colloidal drug delivery approach.

Liposomes are particles made up of phospholipids and cholesterol. This imparts vesicle integrity and helps to achieve a closely packed structure. These liposomes are highly biocompatible and biodegradable and hence have better acceptance when

used in the form of vaccines. They provide a better mucosal, systemic and transcutaneous immunization. In case of trivalent vaccines for H1N1 and H2N2 virus the liposomes are used to enhance the immune recognition.

Niosomes have two layers which are made up of non-ionic surfactants and cholesterol thereby making them more stable and preventing auto-oxidation. They are used to deliver antigens against common virulence causing organisms [34]. However, its response against swine flu virus is under research.

Archaeosomes are self-assembled units prepared by using polar phospholipids which are derived from an archebacteriae known as Sulfolobus acidocaldariu. These are prepared by aggregation of the archebacteriae below its critical micelle concentration [35]. This kind of approach is of great significance while choosing oral route for vaccine administration. It helps in enhancing the mucosal immunization. They are stable at high temperatures, alkaline pH and have better immune adjuvant properties.

Spherulites are vesicles made up of amphiphilic lipids, which are biocompatible and do not show the presence of any aqueous core. They have unique structural configuration which makes them more stable as well as increasing its microencapsulation efficiency [36]. This helps to protect the antigen in the virus from the external environment. Spherulites are commonly used when the parenteral route of vaccine administration is preferred as systemic immunization is enhanced.

Transfersomes are also known as elastic liposomes [37]. They contain phospholipid, cholesterol and an edge activator which is commonly ethanol. The edge activator provides flexibility which allows them to change their shapes and thus provides better penetration. They are used in oral as well as the transdermal route to induce immunity [38]. This approach is used for delivery of vaccines in HIV. Since the virus structure of H1N1 is similar to HIV this approach is being studied to develop a more effective vaccine for swine flu.

Microspheres are spherical in shape and are made up of synthetic and natural biopolymers. They help to impart immunity against infectious diseases when the choice of route is oral administration. The natural polymers like gelatin, pectin, chitosan etc. are used in microspheres. Polylactic acid [PLA], Poly caprolactone is synthetic polymers which are generally used in the preparation of microspheres [39]. It had been discovered that environmentally safe microspheres enclosed with vaccine antigen help to provide long lasting immunity. Since swine flu is a highly progressive disease, hence imparting long-lasting immunity could help hence microsphere approach for its vaccine is being studied [40]. Here the particle size of microspheres decides the immune response; larger particles will not be able to enter the tissues targeted and the optimum particle size required for microspheres is below 125 mm. Biodegradable microspheres are commonly used for mucosal immunization. Microspheres comprising of synthetic polymers like polylactic acid are used when the vaccine delivery is from oral or systemic routes [41]. Microspheres prepared from chitosan are commonly used in vaccines for influenza and are also proved to be successful in nasal route for vaccine delivery in case of influenza where FluMist® is the first nasal vaccine, which had been developed by a company known as Medimmune Inc.

Virus like particles and virosomes consists of viral envelope which is self-assembled and does not have any genetic material and non-infective particles [42]. These types of particles have better permeability through the cellular membranes. They are easy to prepare and have a higher antigen loading capacity. Virosomal vaccines are preferred for influenza. Inflexal® V is the vaccine developed by Berna Biologics [Bern, Switzerland] with virosomes to treat flu symptoms and seasonal flu. Invivac® for nasal flu was developed by Solvay Pharma Registered in the Netherlands, Switzerland uses virosomal approach to treat flu. NasalFlu® for the curing nasal flu was made using virosomes by Berna Biologics Marketed in Switzerland. Virosomes have excellent adjuvant properties which make them evoke better immune recognition.

Protozoans are similar to transmembrane proteins and are hydrophobic in nature. They act as carriers for delivering antigens, polypeptides and lipopolysaccharides. They are commonly used when the nasal route of administration of vaccine is used. They are site-specific hence have a wider range of targets. They adhere to the surface of T-cells and initiate the immune response. They can be used for oral, topical as well as parenteral route of vaccine delivery. Nasal vaccines are highly effective in case of influenza viruses [43]. Hence proteosomal approach can be used to target swine flu virus.

Immuno-potentiating Reconstituted Influenza Virosomal Carriers [IRIVS] are comprised of spherical hexagonal single laminar vesicles. They are safer, non-toxic and free from any adverse reactions. They contain phospholipids along with phosphatidylcholine [PC] and phosphatidylethanolamine [PE] which are the components which help to attain immunity [44]. They are used in the oral mucosal immunization process for influenza HIV. Thereby can be used to target swine flu virus and acquire immunity against it. The vaccine H5N1 virus is prepared with this technique and is administered through the sub-lingual route.

Antigen cochleates contain calcium ions which aid in delivering the antigen. They can be obtained by infusion of calcium ions with the phospholipids and cholesterol. Calcium gives the particles a jelly roll like structure. They have the best compatibility, stability, target species, hence are most preferred. They are used for subunit and multiple unit vaccines, which are administered via oral mucosal, nasal or parenteral route [45]. Cochleates have been used in preparation of vaccines for HIV, which help to boost the mucosal immunity. Hence cochleates are being researched for its ability to impart immunity against swine flu.

The other lipid based carriers available currently involve triglyceride emulsions, micellar systems, solid-lipid nanoparticles

[SLNs] and self-emulsifying drug delivery systems [SEDDS]. These lipids based carriers with the use of gut associated lymphoid tissues can easily enter the lymphoid tissue and induce oral immunization [46]. This type of approach has already been studied for HIV but for swine flu virus this kind of approach is still under development.

Dendrimers are highly branched molecules comprising of various small units known as monomers which are bonded covalently with each other. Each monomer unit is termed as Dendron. The inner part of the dendrimer is hydrophilic, which assists in the encapsulation of vaccine antigens. The external branches are hydrophobic, which eases the penetration in the immune recognition cells. Poly [amidoamine] [PAMAM] dendrimers and Poly [propyleneimine i.e. PPI] are explored for such approach. Since penetration is enhanced using this approach it is being studied for its immunizing activity in case of swine flu [47].

Carbon nanotubes are the allotropes of carbon. These are used for vaccine delivery since it has a very hollow internal structure and greater surface area. They can easily permeate through the membranes and are non-toxic. The surface of the carbon nanotubes is easy for adsorption of antigens. These antigens bind the surface of carbon nanotubes via hydrophobic interactions and Vander Waals forces [48, 49]. These are highly stable molecules they resist degradation and provide controlled release of antigen at specific target sites. This kind of approach might prove to be important in developing swine flu vaccine.

An Inference Drawn from Novel Drug Delivery Approaches for Vaccines

The colloidal carriers aid in effective delivery of vaccines since they have better targeting properties and adjacent properties which enables to develop a stronger immune response against the pathogens. In case of swine flu this type of approach is significant since there is a need to stop the disease from progressing and avoid the emergence of epidemics. This approach provides immunization at a faster rate also drawbacks of the conventional vaccines can be improvised. The vaccines prepared using a novel drug delivery approach has lesser side effects, better penetration ability, and better permeability. Irrespective of the advantages of novel drug delivery approach for vaccines, there is difficulty in the development of such approaches because of tedious and time consuming process.

New approaches for the control of influenza have been illustrated in the **Figure 9** [50,51].

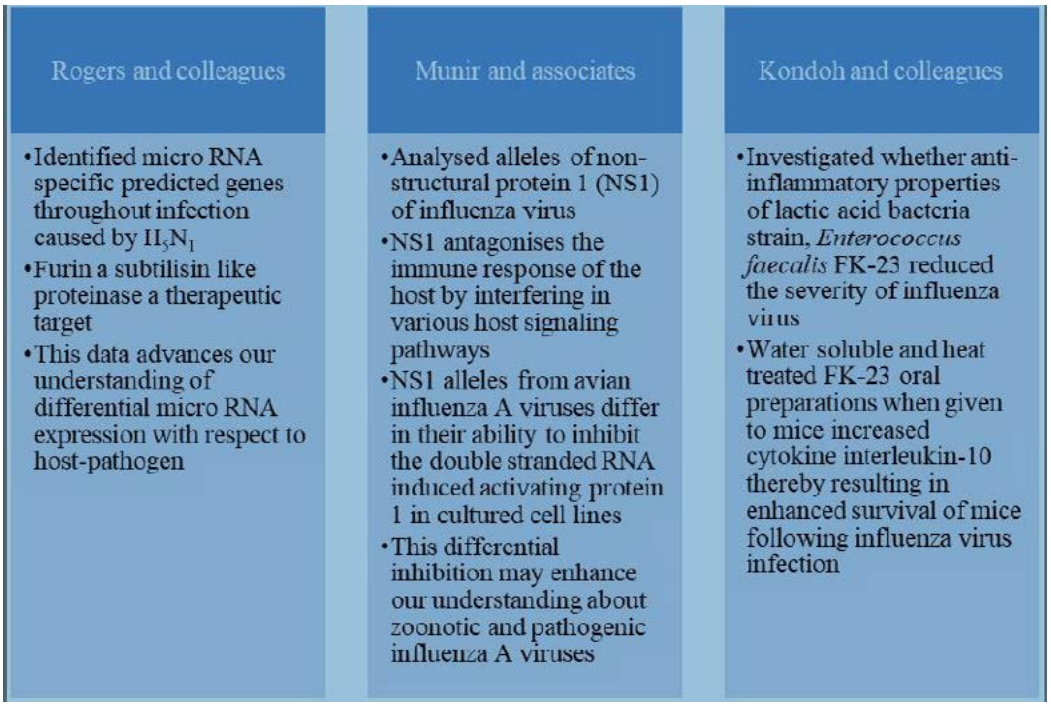

Figure 9. New approaches for the control of influenza.

Current Research Guidelines as per WHO

The most important recommendations regarding the further research were suggested by WHO in the following areas:

- Increased learning to check the capacity of the antivirals and supporting medications which are existing as well as which are under investigation, which also include regional products used for severe complicated influenza illness.

- Usage of post-septic sera/plasma or monoclonal antibodies in problematic illness is because of influenza virus infection by increasing the analysis to assess its efficacy.

- To conduct comparative studies of clinical trials of neuraminidase inhibitors, which are utilized for the medication of influenza for all the populations. Special attention to be provided to the parenteral neuraminidase inhibitors, which are mostly for

critically ill patients, and also enhancing the safety and comparative efficacy.

- The clinical and laboratory virological limitations which are used to evaluate the consequences of such assessments conducted should be standardized.
- Special care to denote dosage, safety and competence of all the antivirals used for the treatment for children under one year and particularly for neonates diagnosed with influenza infection.
- Build-up of administering oseltamivir and zanamivir by different routes, especially for neonates diagnosed with virus infection and for severely ill patients should be encouraged.
- Studies of different combinations that can be used for treatment, longer durations of the dose action in the system, loading of the doses, and higher doses.
- Improved pharmacodynamic and pharmacokinetic studies regarding the correlation between the doses and the routes of administration, and the viral amount in the lower respiratory tract with the influenza infection.
- Accurate knowledge regarding the medication of influenza mainly in gestating females, patients dealing with obesity, the immunosuppressed [in addition to the HIV] infected individuals as well as people in higher risk groups.
- Better definitions to be developed for patients who are at a greater risk for chronic or severe influenza sickness such as HIV infected groups [adults as well as children], pregnant women and obese individuals.
- Progressive studies on the different methods of action and clinical conditions which improves the protection from the antiviral medications is likely to develop.
- Evolution and improvement of a durable surveillance system to monitor the influenza antiviral resistance.

Preventive Measures for Swine Flu

Swine flu is a disease caused by the transmission of the influenza virus H1N1 through different modes which is highly possible in almost every populated city, town or village. A few precautions are bound to be taken at the individual's end to prevent the occurrence of this illness in the system. Some of those measures are listed below [52-56].

Preventive Measures on a General Basis

- Covering mouth and nose while sneezing to prevent contact with the virus present in the air.
- Disposable tissues should be preferred over a handkerchief when suffering from a cold and the tissues should be discarded after its usage.
- Touching eyes, nose or mouth regularly should be avoided as it leads to achieving the possible chances of getting infected.
- Alcohol based hand rub, water or soap should be used to wash hands or a hand sanitizer can also be used.
- Droplet infection is one of the possibilities of transmitting the virus wherein the virus may have been deposited on common objects like electronic devices such as phones, laptops or common, desk, chairs, thus touching too many objects should be avoided and hands should be washed if done so.
- Maintaining a minimum distance of 6 to 10 feet should be kept from the person with flu to avoid the airborne transmission of the virus.
- The surfaces at home should be cleaned frequently if anyone at home is suffering from swine flu to prevent it from spreading to the other individuals at home.
- Patients diagnosed with the flu should be indoors one day post the last episode of the occurrence of fever. [Without the consumption of any fever reducing drugs].
- A person suffering from swine flu must wear a mask and cover their mouth and nose before sneezing and manage hand sanitation before and after touching common objects. Following such methods would help to decrease the spread of the disease to others.
- A surgical mask should be worn if an outbreak of swine flu has occurred in the surrounding area.

Preventive Measures for Children/Infants

- Sanitization of baby items before their use is essential. In the presence of a toddler at home, the door knobs, table tops, sides of the bed, and furniture should be kept clean as they would hold on to these places while taking little steps.
- Toys can be washed in bleaching powder solution to keep them toxin free.
- Tethers should be washed with warm water before offering them to the little one.

- Bed sheets and curtains should be regularly washed in the presence of children at home to avoid airborne transmission of the virus from the deposition of it on such surfaces.
- The nasal area should be kept clean as it is the most sensitive area from where the virus can be inhaled into the system.
- Consumption of foods containing vitamin A and vitamin C should be encouraged in the children since it can help to keep the children safe from a bout of viral attack.
- Zinc supplements and foods rich in zinc such as cereals, nuts, pumpkin seeds and squash seeds should be given to children since zinc helps as an important nutrient to boost up the children's immune system and keep them off from seasonal flu and other illnesses.

Preventive Measures for Pregnant Women

- Changes occurring in a woman's immune system during pregnancy make her susceptible to various infections such as flu and thus special care should be taken to prevent acquiring any symptoms of infection.
- The recommendations for prevention from swine flu in pregnant women are similar to those given for a seasonal flu.
- Sick or potentially infected patients should be separated from the healthy pregnant women in populated places such as hospitals and offices.
- Getting vaccinated is the most important and efficient way to prevent the immune system from acquiring infection.

CONCLUSION

Ever since the occurrence of swine flu virus in Mexico in the year 2009, it has affected many countries in the world within a short span of time. It is a pandemic disease which results in a large number of cases causing burden to the already delicate and overstrained health care services. This was a call for a greater need to improve healthcare services in all the countries to ensure effective health facilities to manage the patient load and decrease the fatality rate. Many conventional systems for treatment such as Chinese, Ayurveda, Homeopathy and Unani systems are used to cure swine flu. Antivirals such as Oseltamivir and zanamivir have been extensively used for the treatment of swine flu, but since the availability, limited supply and knowledge of these drugs is lesser in a few of the developing countries, it has led to the discovery of novel drug delivery systems for the treatment of swine flu. The upcoming vaccines are being developed using various new carriers for colloidal drug delivery like noisome, dendrimers etc., which improves the penetration power, permeability and rate of immunization of the vaccine. The various preventive measures mentioned in the article should be employed to avoid the epidemic of swine flu since "Prevention is better than cure".

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