Abstract
Swine flu or H1N1 influenza is a declared pandemic across the world. Till now it has claimed at least 72 lives. The new mutant H1N1 influenza virus is highly infectious, leads to severe disease and human beings lack immunity to it. Oseltamivir and zanamivir are effective agents, both for treatment and prophylaxis. Government of India has started screening all the international passengers on arrival at the airports and set up laboratories to diagnose the infection. Containment of the viral spread is the topmost priority. The effective vaccine seems to be at least 6 months distant.

Introduction
On the morning of 24th April 2009, we woke up to the breaking news that WHO had issued an alert on ‘Influenza-like illness in the US and Mexico by Swine Influenza A (H1N1) virus not been previously detected in pigs or humans’. Although news of people being affected by Swine Flu in Mexico and some parts of the United states had started trickling in a few weeks before, 18th March 2009 to be precise, one had not imagined that this illness caused by an as yet unidentified strain of the virus would take a toll on so many lives and would reach such pandemic proportions so as to be declared as a worldwide emergency.1

By April 27th, WHO had elevated the pandemic alert from phase 3 to phase 4 and within next few days to phase 6. Pandemic Phases 1–3 correlate with preparedness, including capacity development and response planning activities, while in Phases 5–6 (pandemic), actions shift from preparedness to response at a global level and the goal of recommended actions during these phases is to reduce the impact of the pandemic on society. As of 17 May 2009 this illness is suspected to have affected 8480 people and claimed 72 lives.

Background
Influenza virus infection, one of the most common and highly contagious airborne infectious diseases, causes an acute febrile illness and results in variable degrees of systemic symptoms, ranging from mild fatigue to respiratory failure and death.1

Of the three genera of influenza viruses that cause human flu, two also cause influenza in pigs, with Influenzavirus A being common in pigs and Influenzavirus C being rare. Influenzavirus B has not been reported in pigs. Within Influenzavirus A and Influenzavirus C, the strains found in pigs and humans are largely distinct, although due to reassortment there have been transfers of genes among strains crossing swine, avian, and human species boundaries.

The 1918 flu pandemic in humans was associated with H1N1 and influenza appearing in pigs.2 Although it is not certain in which direction the virus was transferred, pigs to humans or humans to pigs, some evidence suggests that probably pigs caught the disease from humans. The exact origin of the 1918 strain remains elusive.

In 1976 the United States army recruit at Fort Dix died and the next day four of his fellow soldiers were hospitalized. Two weeks after his death it was declared to be due to new strain of swine flu. The strain, a variant of H1N1, is known as A/New Jersey /1976 (H1N1).3 This new strain appeared to be closely related to the strain involved in the 1918 flu pandemic. Moreover, the ensuing increased surveillance uncovered another strain in circulation in the U.S., A/Victoria/75 (H3N2) spread simultaneously, also caused illness, and persisted until March 1976.3

On October 1, 1976, the immunization program against the virus began in the U.S. and by October 11, approximately 40 million people, or about 24% of the population, had received swine flu immunizations. That same day, three senior citizens died soon after receiving their swine flu shots and there was a media outcry linking the deaths to the immunizations, despite the lack of positive proof. This was a strong setback to the program. The National Influenza Immunization Program was halted on December 16, 1976.

There were reports of Guillain-Barré syndrome, a paralyzing neuromuscular disorder, affecting some people who had received swine flu immunizations. This syndrome is a rare side-effect of modern influenza vaccines.4 Overall, there were about 500 cases of Guillain-Barré syndrome (GBS), resulting in death from severe pulmonary complications in 25 people. The vaccine killed more Americans than the disease did.

In September 1988, a swine flu virus killed one pregnant woman and infected others at Wisconsin in the U.S. The only pathogen identified was an H1N1 strain of swine influenza virus.5

In 1998, swine flu was found in pigs in four U.S. states. Within a year, it had spread through pig populations across the U.S. This virus had originated in pigs as a recombinant form of flu strains from birds and humans. This outbreak confirmed that pigs can serve as a host where novel influenza viruses emerge as a result of the reassortment of genes from different strains.1

Current Problem:
2009 Outbreak in Humans
The 2009 flu outbreak is due to a new strain of subtype H1N1 not previously reported in pigs. The new strain was initially described as apparent reassortment of at least four strains of influenza A virus subtype H1N1, including one each from humans and birds, and two from swine. However, subsequent
H1N1 Influenza

H1N1 Virus

Influenza results from infection with one of three basic types of influenza virus viz. A, B, or C, which are classified within the family Orthomyxoviridae. These are structurally and biologically similar single-stranded RNA viruses which vary antigenically. A distinctive feature of influenza viruses is that mutations occur frequently and unpredictably in the eight gene segments, and especially in the hemagglutinin gene. The emergence of an inherently more virulent virus during the course of a pandemic can never be ruled out.

Swine influenza (also called swine flu, hog flu and pig flu) caused by swine influenza virus (SIV), that usually infect pigs and is endemic in pigs. As of 2009 these strains are all found in Influenza C virus and the subtypes of Influenza A virus known as H1N1, H1N2, H3N1, H3N2, and H2N3. Present 2009 flu outbreak in humans, known as “swine flu”, is due to a new strain of influenza A virus subtype H1N1 that contains genes closely related to swine influenza. Pigs can become infected with human influenza viruses and this appears to have happened during the current 2009 flu outbreak.

This virus was originally referred to as swine flu but the WHO decided to rechristen it as ‘Influenza A - H1N1 virus’ on 30th April 2009 in order to avoid confusion over the danger posed by pigs, especially pork consumption by which the disease is not known to occur and to avoid unnecessary slaughter of pigs.

Significant surface proteins of the virus include hemagglutinin and neuraminidase based on which these viruses are typed. These proteins determine the immunogenicity. Influenza A subtype H1N1 expresses hemagglutinin-1 and neuraminidase-1. Infection occurs after transfer of respiratory secretions from an infected individual to an immunologically susceptible individual. If the virus is not neutralized by secretory antibodies, it invades airway and respiratory tract cells. Once it enters the host cells, it leads to cellular dysfunction and degeneration, along with viral replication and release of viral progeny.

Communicability of the virus

A patient is infectious to others from 1 day before to 7 days after the onset of symptoms. If illness persists for more than 7 days, chances of communicability may persist till resolution of illness. Children are likely to spread the virus for a longer period.

H1N1 appears to be more contagious than seasonal influenza. The secondary attack rate of seasonal influenza ranges from 5% to 15%. Current estimates of the secondary attack rate of H1N1 range from 22% to 33%.

Clinical Presentation

After an incubation period of 18-72 hours systemic symptoms ensue due to inflammatory mediators.

The presentation of influenza virus infection varies; however, it usually includes many of the symptoms described below. The overall vulnerability of the population can play a major role. For example, people with underlying chronic conditions, such as cardiovascular disease, hypertension, asthma, diabetes, rheumatoid arthritis, and several others, are more likely to experience severe or lethal infections.

A abrupt onset of illness is common. Fever may vary widely among patients, with some having low fevers (in the 100°F range) and others developing fevers as high as 104°F. Sore throat may be severe and may last 3-5 days associated with rhinitis. Myalgias are common and range from mild to severe. Frontal/retro-orbital headache is common and is usually severe. Ocular symptoms develop in some patients with influenza and include photophobia, burning sensations, and/or pain upon motion. Weakness and severe fatigue may prevent patients from performing their normal activities or work. Cough and other respiratory symptoms may be initially minimal but frequently progress as the infection evolves. Patients may have nonproductive cough, cough-related pleuritic chest pain, and dyspnea. Pulmonary examination may reveal clear lungs or at times rhonchi.

Complications

Common pulmonary complications include primary viral pneumonia, secondary bacterial pneumonia, and exacerbation of COPD and bronchial asthma. Extrapulmonary complications are myositis, rhabdomyolysis, myoglobinuria, myocarditis and pericarditis. At times central nervous system (CNS) complications may arise which include encephalitis, transverse myelitis, and Guillain-Barré syndrome and Reyes syndrome.

Laboratory Studies

Findings of standard laboratory studies such as a CBC count and electrolytes assessment are nonspecific but helpful in the general workup. Leukopenia and relative lymphopenia are typical findings in influenza. Thrombocytopenia may be present.

Specimens for viral studies, viz. RTPCR and viral culture, should be stored at 4°C before and during transportation within 48 hours and at -70°C beyond 48 hours.

Case Definition of H1N1 Influenza

Case definitions of H1N1 influenza are as follows.

Suspected case

A suspected case of swine influenza A (H1N1) virus infection is defined as

A person with acute febrile respiratory illness (fever = 38°C) with onset:

- within 7 days of close contact with a person who is a confirmed case of Swine influenza A (H1N1) virus infection,
- or

- within 7 days of travel to areas where there is one or more confirmed Swine influenza A (H1N1) cases,
Table 1: Dosage of Oseltamivir

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<tr>
<th>Body weight</th>
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<td>For prophylaxis once a day for 10 days</td>
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<td>&lt; 15 kg</td>
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<td>For treatment twice a day for 5 days</td>
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<td>&lt; 15 kg</td>
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<td>15 – 23 kg</td>
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<td>23 – 40 kg</td>
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<td>&gt; 40 kg</td>
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Or

resides in a community where there is one or more confirmed swine influenza cases.

Probable case

A probable case of swine influenza A (H1N1) virus infection is defined as

A person with an acute febrile respiratory illness who:

- is positive for influenza A, but unsubtypable for H1 and H3 by influenza RTPCR or reagents used to detect seasonal influenza virus infection,

Or

is positive for influenza A by an influenza rapid test or influenza immunofluorescence assay (IFA) plus meets criteria for a suspected case,

Or

An individual with a clinically compatible illness who died of an unexplained acute respiratory illness who is considered to be epidemiologically linked to a probable or confirmed case.

Confirmed case

A confirmed case of swine influenza A (H1N1) virus infection is defined as

A person with an acute febrile respiratory illness with laboratory confirmed swine influenza A (H1N1) virus infection at WHO approved laboratories by one or more of the following tests:

- Real time PCR
- Viral culture
- Four-fold rise in swine influenza A (H1N1) virus specific neutralizing antibodies.

For confirmation of diagnosis, clinical specimens such as nasopharyngeal swab, throat swab, nasal swab, wash or aspirate and tracheal aspirate (for intubated patients) are to be obtained. Paired blood samples at an interval of 14 days for serological testing should also be collected.

Pandemic Concerns

The pandemic concerns of H1N1 influenza are because of the following factors. Since this virus is a new strain, human populations have not been vaccinated or naturally immunized. Also, as the viruses reassort (i.e. swap genes) and new viruses that are a mix of swine, human and/or avian influenza viruses emerge, the development of a new vaccine takes time. Widespread human to human transmission occurs with this virus; in contrast, disease transmission in bird flu that peaked in 2006 was almost exclusively from direct contact between humans and birds. Virulence of the H1N1 virus produces severe disease and some deaths. There is a lack of data related to transmission rates, patterns and effectiveness of current influenza treatments and reliable forecasts cannot be made. In Mexico the illness has primarily struck young, healthy adults; whereas most other influenza strains produce the worst symptoms in young children and the elderly.

Treatment

Guiding Principles

The guiding principles are early implementation of infection control, precautions to minimize nosocomial / household spread of disease, prompt treatment to prevent severe illness and death and early identification and follow up of persons at risk.

Critical Measures

Critical measures include the following. Avoid crowding patients together, promote distance between patients. Perform hand hygiene. Wear personal protective equipments which include high efficiency masks (ideally N95 mask or else triple layer surgical mask), gowns, goggles, gloves, cap and shoe cover. If suspected swine flu occurs, isolation is recommended for infected individuals and household contacts. If dedicated isolation room with HEPA filter and negative pressure is not available then patients can be cohorted in a well ventilated isolation ward with beds kept one meter apart.

Antiviral Drug Therapy

The virus isolates in the outbreak have been found resistant to amantadine and rimantadine. The two influenza antiviral drugs approved for use are Oseltamivir and Zanamivir which are neuraminidase inhibitors.

Oseltamivir

Oseltamivir (Tamiflu) is the recommended drug both for prophylaxis and treatment (Table 1). It inhibits neuraminidase, which is a glycoprotein on the surface of influenza virus that destroys an infected cell’s receptor for viral hemagglutinin. The drug must be administered within 48 h of symptom onset.

Oseltamivir is generally well tolerated. Gastrointestinal side effects (transient nausea, vomiting) may increase with increasing doses. Occasionally it may cause bronchitis, insomnia and vertigo. Rarely anaphylaxis and skin rashes may occur. Most frequently reported side effect in children is vomiting. There is no recommendation for dose reduction in patients with hepatic disease. In Indian Market the approximate cost is approximately Rs.2250/- for ten tablets.

Zanamivir

Zanamivir (Relenza) is a sialic acid analogue that potently and specifically inhibits the neuraminidases of influenza A and B viruses. Inhaled zanamivir is effective for the prevention and treatment of influenza virus infections. Early zanamivir treatment (10 mg twice daily for 5 days) of febrile influenza in ambulatory adults and children aged 5 years and older shortens the time to illness resolution by 1 to 3 days and in adults reduces by 40% the risk of lower respiratory tract complications. Zanamivir is inhaled through Diskhaler, an oral inhalation device. This drug is not freely available in India.

Opinions vary on the treatment protocol of diagnosed patients. While European countries have been using Oseltamivir and Zanamivir aggressively to prevent transmission, US and Mexico have been prioritizing, using anti-viral drugs for...
treating people in high risk group like pregnant women or those who have severe disease like HIV. As far as India is concerned, the recently finalized clinical guidelines, any infected person who tests positive for H1N1 infection will be initiated on treatment irrespective of the severity of illness. Indiscriminate use of antibiotics by the medical professionals should be avoided as recommended by WHO.

Resistance can develop to antiviral drugs used for influenza. Therefore, WHO and its partners are monitoring antiviral drug resistance.11

Discharge Policy

Adult patients should be discharged 7 days after symptoms have subsided; whereas children should be discharged 14 days after symptoms have subsided. The family of patients discharged earlier should be educated on personal hygiene and infection control measures at home.

Guidelines on Infection Control Measures

Infection control measures would be targeted according to the risk profile as follows;8,10,13

Prevention of Pig to Human Transmission

The transmission from swine to human occurs mainly in swine farms where farmers are in close contact with live pigs. Farmers and veterinarians are encouraged to use a face mask when dealing with infected animals. The use of vaccines on swine to prevent their infection is a major method of limiting swine to human transmission. Major risk factor that may contribute to swine-to-human transmission include not wearing gloves when working with sick animals.

Health Facility Managing The Human Cases

During Pre-Hospital Care

Standard precautions are to be followed while transporting patient to a health-care facility. The patient should also wear a three-layer surgical mask. Aerosol generating procedures should be avoided during transportation as far as possible. The personnel in the patient’s cabin of the ambulance should wear full complement of personal protective equipment (PPE) including N95 masks, the driver should wear three-layered surgical mask.

Once the patient is admitted to the hospital, the interior and exterior of the ambulance and reusable patient-care equipment needs to be sanitized using sodium hypochlorite or quaternary ammonium compounds. Recommended procedures for disposal of waste (including PPE used by personnel) generated in the ambulance while transporting the patient should be followed.

During Hospital Care

The patient should be admitted directly to the isolation facility and continue to wear a three-layer surgical mask.

The identified medical, nursing and paramedical personnel attending the suspect/probable/confirmed case should wear full complement of PPE (including N95 mask). If splashing with blood or other body fluids is anticipated, a water-proof apron should be worn over the PPE.

Aerosol-generating procedures such as endotracheal intubation, nebulized medication administration, induction and aspiration of sputum or other respiratory secretions, airway suction, chest physiotherapy and positive pressure ventilation should be performed by the treating physician/nurse wearing a full complement of PPE with N95 respirator on. Sample collection and packing should also be done under full cover of PPE.

Perform hand hygiene before and after patient contact and following contact with contaminated items, whether or not gloves are worn.

Until further evidence is available, infection control precautions should continue in an adult patient for 7 days after resolution of symptoms and 14 days after resolution of symptoms for children younger than 12 years because of longer period of viral shedding expected in children.

The virus can survive in the environment for variable periods of time (hours to days). Cleaning followed by disinfection should be done for contaminated surfaces and equipments. The virus is inactivated by a number of disinfectants such as 70% ethanol, 5% benzalkonium chloride (Lysol) and 10% sodium hypochlorite. Patient rooms/areas should be cleaned at least daily and finally after discharge of patient. In addition to daily cleaning of floors and other horizontal surfaces, special attention should be given to cleaning and disinfecting frequently touched surfaces. To avoid possible aerosolization of the virus, damp sweeping should be performed. Horizontal surfaces should be dusted by moistening a cloth with a small amount of disinfectant.

Clean heavily soiled equipment and then apply a disinfectant effective against influenza virus (mentioned above) before removing it from the isolation room/area. If possible, place contaminated patient-care equipment in suitable bags before removing it from the isolation room/area. When transporting contaminated patient-care equipment outside the isolation room/area, use gloves followed by hand hygiene. Use standard precautions and follow current recommendations for cleaning and disinfection or sterilization of reusable patient-care equipment.

All waste generated from influenza patients in isolation room/area should be considered as clinical infectious waste and should be treated and disposed in accordance with national regulations pertaining to such waste. When transporting waste outside the isolation room/area, gloves should be used followed by hand hygiene.

Vaccine

The H1N1 swine flu viruses are antigenically very different from human H1N1 viruses and, therefore, vaccines for human seasonal flu would not provide protection from H1N1 swine flu viruses.14 The seasonal influenza vaccine will likely help provide partial protection against swine H3N2, but not swine H1N1 viruses.

Influenza viruses have the ability to change and mutate, making it difficult to make effective vaccines. About 6 months of time is expected for the new vaccine to come to market.10,14

WHO Response

Balancing Rights, Interests and Values

WHO has a policy to deal with Influenza pandemic. Preparedness planning for influenza pandemic involves balancing potentially conflicting individual and community interests. In emergency situations, the enjoyment of individual human rights and civil liberties may have to be limited in the public interest. Measures that limit individual rights and civil liberties must be necessary, reasonable, proportional, equitable, non-discriminatory, and in full compliance with national and international laws.
Communication strategies should ensure that the public has access to information about: the availability of drugs for treatment and prophylaxis.

The availability of health-care workers will be essential in order to provide an effective response to an influenza pandemic. Therefore countries should develop policies that clearly delineate health-care workers’ obligations.

Goals of Disease Surveillance by WHO

Goals of disease surveillance by WHO are to coordinate the assessment and monitoring of the disease characteristics and severity, and provide guidance accordingly; to monitor the global spread of disease and possible changes in epidemiological, clinical, and virological aspects of infection, including antiviral drug resistance; and to support affected Member States as much as possible in confirming the spread of human infections and assessing the epidemiological situation, trends, and impact.10

Travel Advice

WHO is not recommending travel restrictions related to the outbreak of the influenza A (H1N1) virus. Individuals who are ill should delay travel plans and returning travelers who fall ill should seek appropriate medical care.6,9,15

Antiviral Drug Supply

WHO has set first priority to provide an emergency stock of antiviral drugs to countries that have no or insufficient stock of the drugs and lack the capacity to procure these drugs themselves. WHO is also working with Member States, donors and other groups that have stockpiles and are willing to share these with WHO for distribution to countries in need. WHO had a global stockpile of approximately 5 million adult treatment courses of oseltamivir.11

Indian Scenario

The Government of India has started to screen all people entering India via all the international airports. Primary focus will be on passengers entering from the United States of America, The United Kingdom, Canada, Mexico, France and New Zealand.16

Health screening of passengers coming from affected countries is continuing at 21 International airports. 191 doctors and 101 paramedics have been deployed to man 76 counters at the above airports. Till date about 5.75 lakh passengers have been screened. The Ministry of Health and Family Welfare (MOHFW) is also trying to track down people who have entered India from Mexico in the last month. Surveillance has also been established at ports.

Till 17th May 2009 samples of 59 persons have been tested and 58 found negative for Influenza H1N1. Sample of one person has tested positive for Influenza A (H1N1). He is under observation and recovering well. Samples of two other persons are under testing.16

Indian government is stockpiling on drugs worth Rs. 36-38 crores which will provide up to million doses.

In India four labs have been put on high alert to test human samples for H1N1 infection. These are National Institute of Communicable Diseases, Delhi, National Institute of Virology, Pune, National Institute of Cholera and Enteric Diseases, Kolkata and Regional Medical Research Centre, Dibrugarh. The MOHFW has finalized the protocols for the uniform testing procedures of suspected human samples at National Institute of Virology (NIV), Pune and National institute of Communicable Diseases (NICD), New Delhi.8

Problems for India

If H1N1 influenza comes a big way in India we may face some major problems. Isolation facilities may prove inadequate and containment can be difficult. Due to the overlap of the disease symptoms with other illnesses it may become difficult to identify true cases. The protective mask (N95) which is believed to afford protection against exposure to the virus comes with a high cost. Also the drugs are costly. On top, this disease will have a major social and economic impact on the country.

References