The emergence of influenza A (H1N1) 91 years ago led to a disastrous global pandemic. In the present scenario, the swine-origin influenza A (H1N1) virus (S-OIV) infection, a reassorted influenza virus was first reported from Mexico in March 18, 2009. The spread rapidly occurred to neighboring United States and Canada and from there on to the rest of the world. On April 15 and April 17, 2009, the Centers for Disease Control and Prevention (CDC) identified two cases of human infection with S-OIV characterized by a unique combination of gene segments that had not been identified among human or swine influenza A viruses.

On April 25, 2009, the World Health Organization (WHO) declared a public health emergency of international concern. The emergence of S-OIV infection among humans presents the greatest pandemic threat since the emergence of influenza A (H3N2) virus. India reported its first case on May 13, 2008. Most of the cases reported subsequently were travel-related cases, among those traveling to India from affected countries.

**EMERGENCE OF INFLUENZA A (H1N1) VIRUSES FROM BIRDS AND SWINE INTO HUMANS**

*Figure 1* shows the important events and processes in the emergence of influenza A (H1N1) viruses during the past 91 years. Avian, swine and human populations are represented in the top, middle and bottom of the *Figure 1*, respectively. Epidemic or zoonotic viruses are shown as wide horizontal arrows. The disappearance of H1N1 in 1957 most likely represents competition by the emerging pandemic H2N2 strain in the face of population immunity to H1N1. The reemergence in 1977 is unexplained and probably represents reintroduction to humans from a laboratory source.

**Virus**

It is an enveloped, single stranded ribonucleic acid (RNA) virus with eight segmented genome and mutations occur frequently and unpredictably in the eight gene segments, and more so with the hemagglutinin (HA) gene (*Figure 2*). Point mutations in the HA gene cause minor antigenic changes to HA, which is a continuous process and causes seasonal epidemics by a process called the antigenic drift. Another phenomenon called the antigenic shift leads to the emergence of a novel human influenza A virus subtype through a rapid process of genetic reassortment, which is responsible for the pandemics.

There are three basic types of influenza virus (A, B or C) within the family Orthomyxoviridae. The influenza A subtype H1N1, which expresses the HA-1 and neuraminidase-1 causes the infection when the respiratory secretion from an infected individual is transferred to an immunologically susceptible person. After overcoming the resistance from the secretory antibodies from the respiratory tract, it enters the host cell and leads to cellular dysfunction and degeneration, along with viral replication and release of viral progeny. The transmission occurs by droplet infection and the fomites play a major role in it.

**Communicability**

The incubation period for S-OIV infection appears to range from 2 to 7 days; the patient is infectious from before the 1st day of illness to 7 days after the onset of symptoms. If the illness persists for more than 7 days, chances of communicability may persist till resolution of illness. The secondary attack rate of H1N1 varies from 22% to 33% (*Table 1*).

**CLINICAL FEATURES OF SWINE INFLUENZA**

The clinical spectrum of novel S-OIV infection is still being defined, but both self-limited illness and severe outcomes, including respiratory failure and death, have been observed among identified patients.

The systemic symptoms are manifested after the incubation period of 18–72 hours and it includes fever (low grade to high grade), sore throat with rhinitis, with a minimal cough lasting for a period of 3–5 days and mild to severe myalgia with headache. Ocular symptoms include photophobia, burning sensations, pain on moving the eyelids and the ensuing weakness and severe fatigue might render the patient to bed. Over the course of the disease, they may have nonproductive cough, pleuritic chest pain and dyspnea. Most confirmed cases of S-OIV infection have been characterized by

**TABLE 1 | Persons at risk for influenza**

<table>
<thead>
<tr>
<th>Persons at risk for influenza</th>
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</thead>
<tbody>
<tr>
<td>Age 0–4 years and more than 65 years</td>
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<tr>
<td>Pregnant women</td>
</tr>
<tr>
<td>Chronic metabolic diseases (DM)</td>
</tr>
<tr>
<td>Pulmonary diseases (asthma, COPD)</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
</tr>
<tr>
<td>Renal diseases</td>
</tr>
<tr>
<td>Hemoglobinopathies</td>
</tr>
<tr>
<td>HIV</td>
</tr>
</tbody>
</table>

**Abbreviations:** DM, Diabetes mellitus; COPD, Chronic obstructive pulmonary disease; HIV, Human immunodeficiency virus
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The common pulmonary complications are primary viral pneumonia, secondary bacterial pneumonia (particularly with group A Streptococcus, Staphylococcus aureus, and Streptococcus pneumoniae with frequent exacerbation of underlying chronic obstructive pulmonary disease (COPD) and bronchial asthma. The extrapulmonary complications include myocarditis and pericarditis, myositis, rhabdomyolysis, myoglobinuria, encephalitis, transverse myelitis, Guillain-Barré and Reye’s syndromes.

**Swine Flu in Human Immunodeficiency Virus Patients**

Limited data exist on the immunogenicity of the 2009 influenza A (H1N1) vaccine among immunocompromised persons. A study by Nancy et al. revealed that, despite high CD4 cell counts and receipt of antiretroviral medications, human immunodeficiency virus (HIV) infected adults generated significantly poorer antibody responses, compared with HIV-uninfected persons.

**CASE DEFINITIONS**

A suspected case of pandemic 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 pandemic influenza A (H1N1) virus infection, or within 7 days of travel to a community where there are one or more confirmed pandemic influenza A (H1N1) cases, or resides in a community where there are one or more confirmed pandemic influenza cases.
Infectious Diseases

A probable case of pandemic 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 real-time polymerase chain reaction (RT-PCR) or reagents used to detect seasonal influenza virus infection; or is positive for influenza A by an influenza rapid test or an influenza immunofluorescence assay (IFA); plus, meets the criteria for a suspected individual case with a clinically compatible illness who died of an unexplained acute respiratory illness (ARI) and is considered to be epidemiologically linked to a probable or confirmed case.6

A confirmed case of pandemic influenza A (H1N1) virus infection is defined as a person with an acute febrile respiratory illness with laboratory confirmed pandemic influenza A (H1N1) virus infection at WHO approved laboratories, by one or more of the following tests: RT-PCR or viral culture or four-fold rise in pandemic influenza A (H1N1) virus-specific neutralizing antibodies.6

DIAGNOSIS

The specimens for the specific diagnosis include swabs from the nasal, nasopharyngeal, throat or the tracheal aspirate. The ideal swabs being the ones with the synthetic tips (Figure 3).

The specimen should be obtained within 5 days of symptom onset and transported to the laboratory without delay. If there is a delay, the specimen should be stored at 4°C and the same should be stored at −70°C if the anticipated delay is beyond 48 hours.

The methods involve the use of RT (RT-PCR preferred), isolation of virus by culture and the demonstration of a four-fold rise in virus-specific neutralizing antibodies. The leukocyte counts will be mostly normal, and if there is associated leukocytosis more than 15,000, secondary bacterial infections should be suspected. The rising values of alkaline phosphatase, creatine kinase and thrombocytopenia indicate poor prognosis.

TREATMENT

General Measures

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 (Table 1). Avoid crowding of patients together, promote distance between patients and advocate hand hygiene.6,7

Besides the general measures, rest and adequate hydration should be ensured. Antipyretics: paracetamol or ibuprofen can be used to control fever and care should be taken to avoid the use of salicylates. The patient should be put on supportive oxygen therapy and the needy should be put on mechanical ventilation. Noninvasive ventilation is an option when mechanical ventilation is not available. To reduce spread of infectious aerosols, use of filters on expiratory ports of the ventilator circuit/high-flow oxygen masks is recommended. Immunomodulating drugs have not been found to be beneficial in the treatment of acute respiratory distress syndrome (ARDS) or sepsis-associated multiorgan failure. High-dose corticosteroids, in particular, have no evidence of benefit and there is potential for harm. Low-dose corticosteroids (dexamethasone 200–400 mg/day) may be useful in persisting septic shock [systolic blood pressure (SBP) < 90 mm Hg]. Suspected cases not having pneumonia do not require antibiotic therapy. Antibacterial agents should be administered, if required, as per locally accepted clinical practice guidelines. Patients on mechanical ventilation should be administered antibiotics prophylactically to prevent hospital-associated infections.6,7

Antiviral Drug Therapy

Neuraminidase inhibitor (NAI) antiviral drugs can shorten the duration of uncomplicated influenza when administered early (< 48 hours after illness onset).6 Early NAIs treatment in this population may also decrease the development of serious complications, such as pneumonia, and the need for hospitalization. However, the efficacy and optimal timing of NAI treatment for patients critically ill with influenza have not been clearly established. Several retrospective observational studies have found decreased mortality among hospitalized cases in settings where antiviral treatment was initiated within 4 days after onset of symptoms, including in 50 elderly patients with influenza A (H3N2) virus infection.8

The available approved formulations of NAIs include enteral oseltamivir phosphate and inhaled zanamivir and the investigational intravenous (IV) NAIs include oseltamivir, peramivir and zanamivir. The adamantanes (amantadine, rimantadine) are not used presently due to drug resistance.6

Oseltamivir

Oseltamivir is an NAI, which is usually well-tolerated and the common side effect includes nausea, vomiting and occasionally bronchitis, insomnia and vertigo. Rarely, anaphylaxis and skin rashes may occur. Most frequently reported side effect in children is vomiting (Table 2).

Oseltamivir is also available as syrup (12 mg/mL).

Zanamivir

Zanamivir is a sialic acid analog 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.

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Dosages for treatment twice a day for 5 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>Dosage</td>
</tr>
<tr>
<td>&lt; 15 kg</td>
<td>30 mg</td>
</tr>
<tr>
<td>15–23 kg</td>
<td>45 mg</td>
</tr>
<tr>
<td>24–40 kg</td>
<td>60 mg</td>
</tr>
<tr>
<td>&gt; 40 kg</td>
<td>75 mg</td>
</tr>
</tbody>
</table>

Figure 3: Throat swab
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Zanamivir (inhalational) is used at a dosage of 10 mg twice daily for 5 days. This shortens the time of illness resolution by 1–3 days in children, and in adults, reduces the risk of lower respiratory tract complications by 40%.

In few circumstances where oseltamivir-resistant cases have been reported, IV zanamivir, IV peramivir and IV laninamivir have been used successfully.

The dosage for IV zanamivir is 600 mg IV twice daily for 5 days and dosages should be reduced when there is renal disease.

The dosage for IV peramivir is 300–600 mg once-daily (OD) and dosages should be reduced when there is renal disease.

Patients who responded to treatment after 2–3 days and become totally asymptomatic should be discharged after 5 days of treatment. There is no need for a repeat test. In patients who continue to have symptoms of fever, sore throat, etc. even after the 5th day should continue treatment for 5 more days. If the patient becomes asymptomatic during the course of treatment, there is no need to test further. For patients who continue to be symptomatic even after 10 days of treatment or those cases with respiratory distress and in whom secondary infection is taken care of, and if the patient continues to shed the virus, then resistance of the patients to antivirals should be tested. The dose of antivirals may be adjusted on case to case basis. Adult patients should be discharged 7 days after symptoms have subsided. The family of patients discharged earlier should be educated on personal hygiene and infection control measures at home (Flow charts 1 and 2).

PREVENTION

Chemoprophylaxis

All close contacts of suspected, probable and confirmed cases should be started on chemoprophylaxis. Close contacts include household/social contacts, family members, workplace or school contacts, fellow travelers and all health care personnel coming in contact with suspected, probable or confirmed cases.

Oseltamivir is the drug of choice for the prophylaxis and it should be provided till 10 days after the last exposure (maximum period of 6 weeks) (Table 3).

VACCINE PROPHYLAXIS

There are two vaccines, which are used: one is an inactivated killed vaccine and the other is a live attenuated vaccine. The vaccines are trivalent and made from strains of influenza A (H1N1), influenza A (H3N2) and influenza B.

Inactivated Killed Vaccine

The inactivated killed vaccine is indicated for all patients above 6 months of age and given as an intramuscular dose in the deltoids for adults and older children, and in the gluteal for infants and young children. The adult dosage is a single 0.5 mL injection whereas for those in the age group of 6 months to 8 years, two doses with 4 weeks apart should be administered. Immunity develops within the span of 2 weeks and there is no contraindication for pregnancy and systemic diseases. This vaccine offers a protective efficacy of 50–80%.

Live Attenuated Vaccine

The live attenuated vaccine is indicated for all healthy persons 2–49 years, and is contraindicated in pregnancy and systemic diseases. The vaccine is given through the intranasal route and the immunity is acquired in 7–10 days. It has to be given on an annual basis and it offers a protective efficacy of around 90%, the common side effects of nasal administration include nasal congestion with rare instances of anaphylaxis.

MANAGEMENT OF THE CONTACTS

Close contacts of suspected, probable and confirmed cases should be advised to remain at home (voluntary home quarantine) for at least 7 days after the last contact with the case. Monitoring of fever should be done for at least 7 days. Prompt testing and hospitalization must be done when symptoms are reported.

NOTIFICATION

All suspected cases, clusters of influenza-like illness (ILI)/severe ARI (SARI) cases need to be notified to the State Health Authorities and the Ministry of Health and Family Welfare, Government of India [Director, Electronic Medical Records (EMR) and National Institute of Communicable Diseases (NICD)].

REFERENCES


TABLE 3  Dosages for treatment once-daily (OD) for 10 days

<table>
<thead>
<tr>
<th>Weight</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 15 kg</td>
<td>30 mg OD</td>
</tr>
<tr>
<td>15–23 kg</td>
<td>45 mg OD</td>
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<td>24–&lt; 40 kg</td>
<td>60 mg OD</td>
</tr>
<tr>
<td>&gt; 40 kg</td>
<td>75 mg OD</td>
</tr>
</tbody>
</table>

Abbreviation: OD, once-daily
Infectious Diseases