In recent years there has been much concern and alarm about the possibility of an influenza pandemic caused by a novel virulent strain to which the population has no immunity and which, therefore, may be associated with high mortality rates. Medical, social and scientific reaction toward such an event has been, as demonstrated in the case of avian flu (H5N1), been of intense epidemiological surveillance and preparedness. The influenza pandemic the world was waiting for arrived in April 2009 quite unexpectedly from North America in form of Swine Influenza 2009 A/H1N1 virus. What was new was not just the virus but also the continent of origin (North America, not Asia), the season of origin (spring, not winter), and the cohort at risk for infection and death (children and young adults, not infants and the elderly).

The outbreak was first observed in Mexico in March 2009, with evidence that there had been an ongoing epidemic for months before it was officially recognized as such. In less than sixty days this swine Influenza 2009 A/H1N1 virus rapidly spread across 66 countries in the world causing over 52,000 infections including 231 deaths. After human-to-human transmission was documented in more than three countries of two WHO regions, WHO raised the pandemic alert to phase 6 on 11th June, 2009.

Soon after the outbreak of H1n1 virus in the United States and Mexico in April, the Government of India started screening people coming from the affected countries at airports. The first case of this flu in India was found at the Hyderabad airport on 13 May, when a man traveling from US to India was found H1n1 positive. The transmission of the flu increased dramatically the beginning of August, with the first death due to swine flu being reported in Pune on 4th of August 2009. An intense public panic and media attention put this epidemic in limelight like never before. As of 15 November 2009, 15411 cases of swine flu have been confirmed and 523 deaths have been reported in India. Case clustering has been observed around Delhi, Pune and Bangalore cities with 80 % cases being reported from 14 major cities.

Historically, there have been four to five pandemics of influenza during the 20th century, which have occurred at intervals of 9–39 years. The 1918 pandemic (Spanish flu), caused by worldwide spread of a human influenza A (H1N1) virus, was responsible for 40–50 million deaths. An estimated 4.9 million deaths, representing 2% of the population, occurred in India alone. After the pandemic subsided, sporadic cases of human influenza H1N1 continued to occur worldwide. H1N1 then mysteriously disappeared in 1957, likely due to competition with the emerging pandemic H2N2 strain as well as the development of immunity to H1N1 among populations. On January 1976, an outbreak of a respiratory disease occurred among soldiers in an army base in Fort Dix, New Jersey. 230 individuals had serological evidence of infection and there was one death. A swine virus H1N1 A/New Jersey/76 was identified as the cause of the epidemic that, fortunately, did not extend outside the base. In November 1977, another H1N1 strain re-emerged in the former Soviet Union, Hong Kong, and North-Eastern China. It caused a relatively mild disease, mostly in young people.

The causal agent of this influenza pandemic has been found to be a swine-origin influenza A (H1N1) virus (S-OIV) that is characterized by a unique combination of gene segments that has not been previously identified among human or swine influenza A viruses. Phylogenetic analysis of sequences of all genes of A/California/04/2009, the virus isolated from patients in the recent outbreak in USA, showed that its genome represents a quadruple re-assortment of two swine strains, one human strain, and one avian strain of influenza. The largest proportion of genes in this virus comes from swine influenza viruses (30.6 % from North American swine influenza strains, 17.5 % from Eurasian swine influenza strains), followed by North American avian influenza strains (34.4 %) and human influenza strains (17.5 %).

**CLINICAL FEATURES**

Presentation of influenza virus infection can vary from asymptomatic infection to serious complicated illness that may include exacerbation of other underlying conditions and severe viral pneumonia with multi-organ failure. Studies have shown that 95% of patients with swine influenza A (H1N1) met the case definition for influenza-like illness (subjective fever plus cough and/or sore throat). However a recent analysis of patients with documented 2009 H1N1 influenza have shown that fever was absent in 50% of outpatients and in 15 to 30% of patients who were hospitalized giving rise to some controversy. Since a wide range of pathogens can cause influenza-like illness, a clinical diagnosis of influenza should be guided by epidemiologic data and confirmed by laboratory tests.
**CLINICAL CASE DEFINITION**

As swine flu is a notifiable disease, WHO has published case definitions of confirmed and probable diseases as given below:

A **Confirmed case** of swine influenza A (H1N1) virus infection is defined as an individual with laboratory confirmed swine influenza A(H1N1) virus infection by one or more of the following tests:

- Real-time Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR)
- Viral culture
- Four-fold rise in swine influenza A(H1N1) virus specific neutralizing antibodies.

A **Probable case** of swine influenza A(H1N1) virus infection is defined as an individual with an influenza test that is positive for influenza A, but is unsubtypeable by reagents used to detect seasonal influenza virus infection or an individual with a clinically compatible illness or who died of an unexplained acute respiratory illness who is considered to be epidemiologically linked to a probable or confirmed case.

The test(s) should be performed according to the most currently available guidance of testing (http://www.who.int/csr/disease/swineflu/en/index.html) and at WHO certified labs.

**TRANSMISSION**

Transmission of swine influenza A (H1N1) is being studied as part of the ongoing outbreak investigation, but limited data are available. These data indicate that this virus is transmitted from person to person primarily through large-particle respiratory droplet transmission (e.g., when an infected person coughs or sneezes near a susceptible person). Transmission via large-particle droplets requires close contact between source and recipient persons because droplets do not remain suspended in the air and generally travel only a short distance (< 6 feet). Contact with...
contaminated surfaces is another possible source of transmission as well as transmission via droplet nuclei (also called “airborne” transmission). Because data on the transmission of swine H1N1 viruses are limited, the potential for ocular, conjunctival, or gastrointestinal infection is unknown. All respiratory secretions and bodily fluids (diarrheal stool) of swine influenza A (H1N1) cases should be considered potentially infectious till further studies are available.

**INCUBATION PERIOD**

The estimated incubation period is unknown and could range from 1-7 days, more likely 1-4 days.

**DURATION OF VIRUS SHEDDING & INFECTIVITY**

The duration of shedding with swine influenza A (H1N1) virus is unknown. Patients should be considered potentially infectious from one day before to 7 days following onset of illness. Some persons who are infected might be contagious for longer periods (e.g. young infants, immunosuppressed persons and critically ill). Patients should be considered contagious till fever subsides.

**WHOM TO TEST**

Clinicians should test persons for the swine influenza (H1N1) virus if they have an acute febrile respiratory illness or sepsis-like syndrome. Certain groups may have atypical presentations including infants, elderly and persons with compromised immune systems. Priority for testing includes persons who require hospitalization or are at high-risk for severe disease (discussed later). Not all people with suspected swine influenza (H1N1) infection need to have the diagnosis confirmed, especially if the person resides in an affected area or if the illness is mild. Recommendations on who to test may differ by state or community. Specific guidelines about priority testing have been enforced in many countries including most of the states of India due to paucity of testing facility and cost constraints.

**HOW TO TEST: PREFERRED RESPIRATORY SPECIMEN**

Clinicians or qualified microbiologist should obtain an upper respiratory specimen to test for swine influenza A (H1N1) virus with proper precautions. The following should be collected as soon as possible: nasopharyngeal swab, nasal aspirate or a combined nasopharyngeal swab with oropharyngeal swab. If these specimens cannot be collected, a nasal swab or oropharyngeal swab is acceptable. For patients who are intubated, an endotracheal aspirate should also be collected. Bronchoalveolar lavage (BAL) and sputum specimens are also acceptable. The performance of rRT-PCR assays specific for 2009 H1N1 influenza have not yet been established for bronchoalveolar lavage and tracheal aspirates. The sample should be collected preferably before administration of the anti-viral drugs.

**SWABS**

Ideally, swab specimens should be collected using swabs with a synthetic tip (e.g. polyester or Dacron) and an aluminum or plastic shaft. Swabs with cotton tips and wooden shafts are not recommended. Specimens collected with swabs made of calcium alginate are not acceptable. The swab specimen collection vials should contain 1-3ml of viral transport medium (e.g. containing, protein stabilizer, antibiotics to discourage bacterial and fungal growth, and buffer solution).

**SPECIMEN TRANSPORT**

Specimens should be placed into sterile viral transport media (VTM) and immediately placed on ice or cold packs or at 4°C (refrigerator) for transport to the laboratory. All respiratory specimens should be kept at 4°C for no longer than 72 hours before testing and ideally should be tested within 24 hours of collection. If storage longer than 72 hours is necessary, clinical specimens should be stored at -70°C. Freezing at higher temperatures (e.g. -20°C) can reduce the likelihood of virus detection.

**RECOMMENDED TESTS**

Real-time RT-PCR is the recommended test for confirmation of swine influenza A (H1N1) case. Currently, swine influenza A (H1N1) virus will test positive for influenza A and negative for H2 and H3. Specific primers are available for by real-time RT-PCR. If reactivity of real-time RT-PCR for influenza A is strong (e.g. Ct <30) it is more suggestive of a swine influenza A (H1N1) virus. Real-time RT-PCR for H1N1 influenza virus should only be performed in BSL-3 laboratory. Currently, it is being done in around 53 government and private laboratory. Detailed list is available at ministry of health website (http://mohfw-h1n1.nic.in/Laboratories.html)

**OTHER INFLUENZA TESTS**

**RAPID INFLUENZA ANTIGEN TEST**

Some commercially available rapid tests can distinguish between influenza A and B viruses. However, it is not possible to differentiate from seasonal influenza A viruses. These tests have a variable sensitivity (range 10 – 70%) for detecting 2009 H1N1 influenza when compared with rRT-PCR, and a negative result does not rule out influenza virus infection. RIATs have a high specificity (>95%). Therefore, a negative rapid test could be a false negative and should not be assumed a final diagnostic test for swine influenza A (H1N1) virus infection.

**IMMUNOFLUORESCENCE (DFA OR IFA)**

Immunofluorescence depends upon the quality of a clinical specimen, operator skills and has variable sensitivity (range 47 – 93%) in clinical specimens. Therefore, a negative IF could be a false negative and should not be assumed a final diagnostic test for swine
influenza A (H1N1) virus infection. Direct immunofluorescence assays (DFAs) are widely available for 2009 H1N1 influenza virus, have a high specificity (≥96%) and give rapid results. These tests can distinguish between influenza A and B viruses. However, it is not possible to differentiate from seasonal influenza A viruses when influenza viruses are circulating in a community, the positive predictive value of RIDT and DFA tests are generally high and positive test result indicates that influenza virus infection is likely. These tests are very useful in epidemic settings when transmission of the virus is established in the community.

### VIRAL CULTURE

Isolation of swine influenza A (H1N1) virus is diagnostic of infection, but may not yield timely results for clinical management. A negative viral culture does not exclude infection with swine influenza A (H1N1) virus. It is available at selected places and more useful for research and epidemiological purposes.

### SEROLOGICAL TESTING

Though Four-fold rise in swine influenza A (H1N1) virus specific neutralizing antibodies on paired acute- (within 1 week of illness onset) and convalescent-phase (collected 2-3 weeks later) sera is included in the diagnostic criteria of confirmed case of H1N1 infection, it is not advisable. Serologic testing is limited to epidemiological and research studies and is not routinely available through clinical laboratories. It should not be used to guide clinical decisions. Its importance lies in retrospective diagnosis for epidemiological and surveillance purposes.

### WHOM TO TREAT

Clinical judgment is an important factor in treatment decisions. Most patients who have had 2009 H1N1 virus infection had a self-limited respiratory illness similar to typical seasonal influenza. Most healthy persons who develop suspected or confirmed 2009 H1N1 influenza and present with an uncomplicated febrile illness generally do not require antiviral treatment. In addition, persons who appear to be recovering from influenza generally do not require antiviral treatment. However, some groups appear to be at increased risk of influenza-related complications. This includes:

1. People with more severe illness, such as those hospitalized with suspected or confirmed influenza
2. People with suspected or confirmed influenza who are at higher risk for complications
   - Children younger than 2 years old
   - Adults 65 years and older
   - Pregnant women and women up to 2 weeks postpartum (including pregnancy loss)
3. Persons with the following conditions:
   - Chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, hematological or metabolic disorders (including diabetes mellitus).
   - Disorders that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk for aspiration.
   - Immunosuppression, including by medications or by HIV.
4. People younger than 19 years of age who are receiving long-term aspirin therapy
5. Patients with morbid obesity, and perhaps obesity.

Treatment is recommended for all hospitalized patients with confirmed, probable or suspected 2009 H1N1 influenza. Early empiric treatment should be considered for outpatients who are at higher risk for influenza-related complications as mentioned above. Clinical judgment should be used in deciding whether outpatients with risk factors for influenza-related complications require treatment.

### WHEN TO START TREAT

Once the decision to administer antiviral treatment is made, treatment with should be initiated as soon as possible after the onset of symptoms. Recent H1N1 influenza treatment trials have shown benefits from antiviral treatment are best when treatment is started within 48 hours of illness onset. However, some studies of oseltamivir treatment have indicated benefit even for patients whose treatment was started more than 48 hours after illness onset. When treatment is indicated, physician should not wait for laboratory confirmation of influenza because laboratory testing can delay treatment and a negative rapid test for influenza does not rule out influenza. The recommended duration of treatment is five days. Hospitalized patients with severe infections (such as those with prolonged infection or who require intensive unit care admission) might require longer treatment courses.

### Table 1: Comparison of Available Influenza Diagnostic Tests

<table>
<thead>
<tr>
<th>Influenza Diagnostic Tests</th>
<th>Method</th>
<th>Availability</th>
<th>Typical Processing Time</th>
<th>Sensitivity for 2009 H1N1 Influenza</th>
<th>Distinguishes 2009 H1N1 from other influenza A viruses?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid influenza diagnostic tests (RIDT)</td>
<td>Antigen detection</td>
<td>Wide</td>
<td>0.5 hour</td>
<td>10 – 70%</td>
<td>No</td>
</tr>
<tr>
<td>Direct and indirect immunofluorescence assays (DFA and IFA)</td>
<td>Antigen detection</td>
<td>Wide</td>
<td>2 - 4 hour</td>
<td>47-93%</td>
<td>No</td>
</tr>
<tr>
<td>Viral isolation in tissue cell culture</td>
<td>Virus isolation</td>
<td>Limited</td>
<td>2 - 10 days</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>Nucleic acid amplification tests (including rt-PCR)</td>
<td>RNA detection</td>
<td>Limited</td>
<td>48 – 96 hours</td>
<td>86 – 100%</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Currently circulating 2009 H1N1 viruses are susceptible to neuraminidase inhibitors oseltamivir and zanamivir, but resistant to M2 inhibitors amantadine and rimantadine. In clinical trials with H1N1 influenza, oseltamivir and zanamivir drugs have been shown to reduce the symptoms and duration of illness and also prevent severe disease and death. Oseltamivir is used as capsule whereas Zanamivir is available as inhalation Powder. Inhaled zanamivir is contraindicated in persons with chronic pulmonary disease and is not approved in persons aged <7 years. The commercial zanamivir formulation (Relenza®) is a mixture of zanamivir and lactose drug carrier. This formulation is not designed or intended to be used in any nebulizer or mechanical ventilator as there is a risk that lactose can obstruct proper functioning of mechanical ventilator equipment. Detailed dosing is given in table 2.

In patients with pneumonia or severe lower respiratory tract disease, some experts recommend a higher oseltamivir dose (150 mg twice daily in adults) and longer duration of treatment (10 days versus 5 days) because of decreased enteral absorption among critically ill patients and high and prolonged viral replication in the lower respiratory tract. Clinical trials evaluating the efficacy of higher dose and longer duration of oseltamivir therapy for critically ill influenza patients are not yet been completed and dose recommendations may change once the trials are completed.

Peramivir is an investigational NAI available in IV formulation, whose efficacy and safety have not yet been established. The FDA has issued an EUA to allow the use of peramivir to treat suspected or laboratory confirmed 2009 H1N1 influenza patients for whom therapy with an IV agent is clinically appropriate, based upon one or more of the following reasons:

1. Patient not responding to either oral or inhaled antiviral therapy.
2. Drug delivery by a route other than IV (e.g. enteral oseltamivir or inhaled zanamivir) is not expected to be dependable or is not feasible.
3. Clinician judges IV therapy is appropriate due to other circumstances

Dosage for peramivir is 600 mg administered intravenously once daily for 5 to 10 days.

**HOSPITALIZATION**

One of the most controversial issues is the question of hospitalization for H1N1 infection. Hospitalization is often deemed necessary because of the need for isolation of these patients. However in this phase of the pandemic (phase 6), most national and international guidelines recommend that individuals with suspected flu be treated at home. In case of any of the emergency warning signs or deterioration hospitalization is required. For patients at high risk for developing influenza complications, hospital admission should be considered.

**TREATMENT OPTIONS**

Table 2: Antiviral medication dosing recommendations for treatment or chemoprophylaxis of 2009 H1N1 infection. (Table extracted from product information for Tamiflu® and Relenza®)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Treatment (5 days)</th>
<th>Chemoprophylaxis (10 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oseltamivir Adults</td>
<td>75-mg capsule twice per day</td>
<td>75-mg capsule once per day</td>
</tr>
<tr>
<td>Children ≥ 12 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body Weight (kg)</td>
<td>Body Weight (lbs)</td>
<td></td>
</tr>
<tr>
<td>≤ 15 kg</td>
<td>≤ 33 lbs</td>
<td>30 mg twice daily</td>
</tr>
<tr>
<td>&gt; 15 kg to 23 kg</td>
<td>&gt; 33 lbs to 51 lbs</td>
<td>45 mg twice daily</td>
</tr>
<tr>
<td>&gt; 23 kg to 40 kg</td>
<td>&gt; 51 lbs to 88 lbs</td>
<td>60 mg twice daily</td>
</tr>
<tr>
<td>&gt; 40 kg</td>
<td>&gt; 88 lbs</td>
<td>75 mg twice daily</td>
</tr>
<tr>
<td>Zanamivir Adults</td>
<td>10 mg (two 5-mg inhalations) twice daily</td>
<td>10 mg (two 5-mg inhalations) once daily</td>
</tr>
<tr>
<td>Children (≥ 7 years or older for treatment, ≥ 5 years for chemoprophylaxis)</td>
<td>10 mg (two 5-mg inhalations) twice daily</td>
<td>10 mg (two 5-mg inhalations) once daily</td>
</tr>
</tbody>
</table>

**TREATMENT OF INFuenza WHEN OSeltAMIVIR-RESISTANT VIRuses ARE CIRCUlATING**

Although rare, sporadic cases of 2009 H1N1 influenza with resistance to oseltamivir have been reported, Oseltamivir resistance is very common among seasonal influenza A (H1N1) viruses (99.6% of the 2008 seasonal H1N1 flu strains according to the CDC) and prospect of H1N1 developing resistance to Oseltamivir in future is indeed high. Because determination of oseltamivir treatment failure is difficult based on clinical criteria alone, virological testing (rRT-PCR or viral culture) to confirm on-going viral replication may help inform antiviral treatment decisions in critically ill patients. Oseltamivir resistance is
Swine Flu: Current Perspective in 2010

Associated with substitution H275Y in neuraminidase.

Patients with oseltamivir-resistant influenza virus infection should be treated with an antiviral agent to whom the virus is known or suspected to be susceptible (e.g., zanamivir). Peramivir should not be used for treatment of oseltamivir-resistant 2009 pandemic influenza A.

**ANTIVIRAL CHEMOPROPHYLAXIS**

In phase 6 of influenza epidemic, Post exposure antiviral chemoprophylaxis with either oseltamivir or zanamivir can be considered for the following:

1. Persons who are at higher risk for complications and are a close contact of a person with confirmed, probable, or suspected 2009 H1N1 influenza during that person’s infectious period.

2. Healthcare personnel, public health workers, or first responders who have had a recognized, unprotected close contact exposure to a person with confirmed, probable, or suspected 2009 H1N1 influenza during that person’s infectious period.

Antiviral agents should not be used for post exposure chemoprophylaxis in healthy children or adults based on potential exposures in the community, school, camp or other settings. Chemoprophylaxis generally is not recommended if more than 48 hours have elapsed since the last contact with an infectious person or when contact occurred before or after the ill person’s infectious period. Duration of post-exposure chemoprophylaxis is 10 days after the last known exposure to 2009 H1N1 influenza. The dosage is mentioned in Table 2.

Chemoprophylaxis with oseltamivir has been seen to lead to increased incidence of oseltamivir resistant infections. An emphasis on early recognition of illness and treatment as an alternative to chemoprophylaxis after a suspected exposure has recently been proposed. This is especially relevant in healthy vaccinated persons, including healthcare workers, after a suspected exposure.

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**Table 3: Influenza A (H1N1) 2009 monovalent vaccines currently approved for use**

<table>
<thead>
<tr>
<th>Vaccine type</th>
<th>Manufacturer</th>
<th>Presentation</th>
<th>Mercury content (µg Hg/0.5 mL dose)</th>
<th>Age group</th>
<th>No. of doses</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactivated†</td>
<td>Sanofi Pasteur</td>
<td>0.25 mL prefilled syringe</td>
<td>0</td>
<td>6–35 month</td>
<td>2†</td>
<td>Intra-muscular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.5 mL prefilled syringe</td>
<td>0</td>
<td>≥36 mos</td>
<td>1 or 2†</td>
<td>Intra-muscular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.0 mL multidose vial</td>
<td>25.0</td>
<td>≥6 mos</td>
<td>1 or 2†</td>
<td>Intra-muscular</td>
</tr>
<tr>
<td>Inactivated†</td>
<td>Novartis Vaccines and Diagnostics Limited</td>
<td>5.0 mL multidose vial</td>
<td>25.0</td>
<td>≥4 yrs</td>
<td>1 or 2†</td>
<td>Intra-muscular</td>
</tr>
<tr>
<td>Inactivated†</td>
<td>CSL Limited</td>
<td>0.5 mL prefilled syringe</td>
<td>0</td>
<td>≥18 yrs</td>
<td>1</td>
<td>Intra-muscular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.0 mL multidose vial</td>
<td>24.5</td>
<td>≥18 yrs</td>
<td>1</td>
<td>Intra-muscular</td>
</tr>
<tr>
<td>LAIV¶</td>
<td>Medimmune LLC</td>
<td>0.2 mL sprayer††</td>
<td>0</td>
<td>2–49 yrs</td>
<td>1 or 2†</td>
<td>Intranasal</td>
</tr>
</tbody>
</table>

0.5 mL dose contains 15 µg hemagglutinin of A/California/7/2009 (H1N1)pdm.
† Two doses administered approximately 4 weeks apart (≥21 days acceptable) are recommended for children aged 6 months through 9 years. Live attenuated influenza vaccine. A 0.2 mL dose contains 106.5–7.5 fluorescent focal units of live attenuated influenza virus reassortants of A/California/7/2009 (H1N1)pdm.
†† Two doses administered approximately 4 weeks apart are recommended for children aged 2 through 9 years of age.

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**2009 H1N1 INFLUENZA VACCINE**

Influenza vaccines are one of the most effective ways to protect people from contracting illness during influenza epidemics and pandemics. On September 15, 2009, four influenza vaccine manufacturers CSL Limited, Novartis, Sanofi Pasteur & MedImmune LLC received approval from FDA for use of influenza A (H1N1) 2009 vaccines in the prevention of influenza caused by the 2009 pandemic influenza A (H1N1) virus. Both Live attenuated and inactivated influenza A (H1N1) 2009 monovalent vaccine formulations are available. A separate seasonal influenza vaccine will also need to be administered for the 2009/2010 influenza season along with this.

**INACTIVATED VACCINE: DOSAGE, ADMINISTRATION, AND STORAGE**

The composition of the influenza A (H1N1) 2009 monovalent inactivated influenza vaccine varies according to manufacturer, and package inserts should be consulted. Inactivated vaccine should be stored at 35°F to 46°F (2°C to 8°C) and should not be frozen. Inactivated vaccine that has been frozen should be discarded. Dosage recommendations and schedules vary according to age group (Table 4). The intramuscular route is recommended for administering the influenzaA(H1N1)2009 monovalent inactivated vaccine. Adults and older children should be vaccinated in the deltoid muscle. Infants and young children should be vaccinated in the antralateral aspect of the thigh.

**LIVE ATTENUATED INFLUENZA VACCINE (LAIV): DOSAGE, ADMINISTRATION, AND STORAGE**

LAIV is made from an attenuated virus that is able to replicate efficiently only at temperatures present in the nasal mucosa. LAIV does not cause systemic symptoms of influenza in vaccine recipients, although a minority of recipients experience nasal congestion or fever. LAIV does not contain thimerosal. LAIV is intended for intranasal administration only and should not be administered by the intramuscular, intradermal or intravenous route. LAIV is not licensed for vaccination of children younger...
than 2 years or adults older than 49 years of age. LAIV should not be administered to persons with asthma. LAIV is supplied in a prefilled, single-use sprayer containing 0.2 mL of vaccine. Approximately 0.1 mL (half) is sprayed into the first nostril while the recipient is in the upright position. An attached dose-divider clip is removed from the sprayer to administer the second half of the dose into the other nostril while then recipient is in the upright position. LAIV should be stored at 35°F to 46°F (2°C to 8°C) and can remain at that temperature until the expiration date is reached.

WHOM TO ADMINISTER

WHO and CDC's Advisory Committee on Immunization Practices has made recommendations for which persons should be the initial targets for immunization with influenza A (H1N1) 2009 monovalent vaccines. The initial target groups include:

- Children aged 6 months to 19 years
- Pregnant women
- People 50 years of age and older
- People of any age with certain chronic medical conditions
- People who live in nursing homes and other long-term care facilities
- People who live with or care for those at high risk for complications including:
  - Health care workers
  - Household contacts of persons at high risk for complications from the flu
  - Household contacts of children less than 6 months of age.

The immunization should be extended to everyone once the demand for vaccine for the target groups has been met.

CAUTIONS

The 2009 (H1N1) monovalent LAIV has the same age range for use as the seasonal LAIV and should not be used to vaccinate children aged <2 years, adults aged >49 years, pregnant women, persons with underlying medical conditions that confer a higher risk for influenza complications, or children aged <5 years old with one or more episodes of wheezing in the past year. The age groups, precautions, and contraindications approved for the influenza A (H1N1) 2009 monovalent vaccine are identical to those approved for seasonal vaccines. Local discomfort (e.g., injection site tenderness or pain) was reported by 46% of subjects during the trials and one or more systemic symptoms (e.g., headache, malaise, or myalgia) by 45% of subjects. The safety profile is consistent with results from studies of the seasonal influenza vaccine.

There is a great concern related to the fast-track approval processes for the H1N1 vaccine granted by many regulatory bodies. Emergence of swine influenza epidemic at Fort Dix in 1976 led to the implementation of a mass vaccination program with fast tracked vaccine, with 40 million civilian vaccinations. Following the vaccination, there were 532 cases of the Guillain-Barre syndrome and 32 deaths. The mass vaccination campaign was then stopped and the vaccine was withdrawn. Most of the regulatory bodies have advised caution and surveillance for all side effects.

CURRENT STATUS OF PRODUCTION OF H1N1 VACCINES IN INDIA

Three manufactures Serum Institute of India Ltd, Panacea Biotech, Bharat Biotech were given license by DCGI to import the WHO approved seed strains and they are in different stages of development. India is currently targeting inactivated vaccine only. The vaccines are in various stages of animal trials only and human trials are not expected to end before February 2010.

PERSONAL PRECAUTIONS TO REDUCE 2009 INFLUENZA A (H1N1) VIRUS TRANSMISSION.

In areas with confirmed human cases of 2009 influenza A (H1N1) virus infection, the risk for infection can be reduced through a combination of actions. No single action will provide complete protection, but an approach combining the following steps can help decrease the likelihood of transmission. These recommended actions are:

1. Wash hands frequently with soap and water. If soap and water are not available, use an alcohol-based hand rub.
2. Cover your mouth and nose with a tissue when coughing or sneezing.
3. Avoid touching eyes, nose and mouth with unwashed hands.
4. People who are sick with an influenza-like illness should stay home and keep away from others as much as possible; including avoiding travel, for at least 24 hours after fever is gone (Fever should be gone without the use of fever-reducing medicine).
5. Avoid close contact (i.e. being within about 6 feet) with persons with ILI.

In addition, influenza antiviral medications and vaccinations are an important tool for the treatment and prevention of 2009 H1N1 influenza. Recommendations for the use of facemasks / respirators are discussed below.

FACEMASK AND RESPIRATOR USE

Information on the effectiveness of facemasks and respirators for decreasing the risk of 2009 H1N1 influenza infection in community settings is extremely limited. Thus, it is difficult to assess their potential effectiveness in decreasing the risk of 2009 influenza A (H1N1) virus transmission. Facemasks do not seal tightly to the face and are used to block large droplets from coming into contact with the wearer's mouth or nose. Most respirators
Table 4: CDC Recommendations for Facemask and Respirator Use for Non-ill Persons to Prevent Infection with 2009 H1N1 and self protection.

<table>
<thead>
<tr>
<th>Setting</th>
<th>Community</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persons at increased risk of severe illness</td>
<td>Facemask/respirator not recommended</td>
</tr>
<tr>
<td>(Non-high risk persons)</td>
<td>Facemask/respirator not recommended</td>
</tr>
<tr>
<td>2009 H1N1 in community</td>
<td>Facemask/respirator not recommended</td>
</tr>
<tr>
<td>2009 H1N1 in community: Not crowded setting</td>
<td>Facemask/respirator not recommended</td>
</tr>
<tr>
<td>2009 H1N1 in community: crowded setting</td>
<td>Facemask/respirator not recommended</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Setting</th>
<th>Home</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persons at increased risk of severe illness</td>
<td>Facemask/respirator not recommended</td>
</tr>
<tr>
<td>(High risk persons)</td>
<td>Facemask/respirator not recommended</td>
</tr>
<tr>
<td>Caregiver to person with influenza-like illness</td>
<td>Avoid being caregiver. If unavoidable, use facemask or respirator</td>
</tr>
<tr>
<td>Other household members in home</td>
<td>Facemask/respirator not recommended</td>
</tr>
<tr>
<td>2009 H1N1 in community</td>
<td>Facemask/respirator not recommended</td>
</tr>
<tr>
<td>No 2009 H1N1 in community</td>
<td>Facemask/respirator not recommended</td>
</tr>
<tr>
<td>Occupational (non-health care)</td>
<td>Facemask/respirator not recommended</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Setting</th>
<th>Occupational (health care)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persons at increased risk of severe illness</td>
<td>Respirator</td>
</tr>
<tr>
<td>(High risk persons)</td>
<td>Consider temporary Reassignment if not, Respirator</td>
</tr>
<tr>
<td>2009 H1N1 in community</td>
<td>Facemask/respirator not recommended</td>
</tr>
<tr>
<td>No 2009 H1N1 in community</td>
<td>Facemask/respirator not recommended</td>
</tr>
</tbody>
</table>

Table 5: CDC Interim Recommendations for Face-mask Use for Persons with Confirmed, Probable or Suspected 2009 Influenza A.

<table>
<thead>
<tr>
<th>Setting</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home (when sharing common spaces with other household members)</td>
<td>Facemask preferred, if available and tolerable, or tissue to cover cough/sneeze</td>
</tr>
<tr>
<td>Health care settings (when outside of patient room)</td>
<td>Facemask preferred</td>
</tr>
<tr>
<td>Non-health care setting</td>
<td>Facemask preferred, if available and tolerable, or tissue to cover cough/sneeze</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>Facemask preferred, if available and tolerable, or tissue to cover cough/sneeze</td>
</tr>
</tbody>
</table>

(e.g. N95) are designed to seal tightly to the wearer’s face and filter out very small particles that can be breathed in by the user. It has been demonstrated that N95 respirators filter out 95 to 99% of relevant aerosol particles while triple layer surgical mask allows penetration of maximum aerosol particles ranging from 4 to 90% in different studies.

Masks or Respirators for Healthcare Workers.

Health care workers have long relied on triple layer surgical masks to provide protection against influenza and other infections. Yet there are no convincing scientific data that support the effectiveness of masks for respiratory protection. These masks may be useful in source control when worn by a patient, but even then, there is evidence that material escapes around the mask’s margins after a sneeze or forcible cough. By contrast, respirators cover the nose and mouth and are designed to purify the air that the wearer breathe in. Until more data are available, clinicians should use N95 respirator when confronting patients with influenza-like illnesses, particularly in enclosed spaces.

Future Direction: Drugs in Development

As seen with other influenza strains, HIN1 influenza viruses will also probably develop resistance to antiviral agent very soon. Treatment with several compounds that act at different stages of the viral life cycle would be more effective and make it less likely that any single mutation could confer resistance. Following drugs are in various stages of development:

Intravenous zanamivir: Especially useful for patients hospitalized with severe influenza and for those in whom neither oral nor inhaled routes are an option.

Long-acting inhaled neuraminidase inhibitors: A therapy based on the enhanced potency of dimeric derivatives of zanamivir. Administration may be possible in a single dose for treatment or once a week for prophylaxis.

Fludase (DAS181): A sialidase fusion construct that cleaves the sialic acid receptors that influenza viruses use for attachment, removing influenza receptors from the airway epithelium and preventing infection of lung cells.

Cyanovirin-N: A hemagglutinin inhibitor that may block viral entry.

T-705: A substituted pyrazine compound that is active against neuraminidase-inhibitor- resistant and amantadine-resistant viruses and that probably inhibits the RNA polymerase.

The recent discovery of the active site of a key endonuclide activity in the PA subunit of the influenza polymerase molecule could lead to a new class of drugs targeting the essential polymerase function of “cap-snatching.” Other promising avenues under investigation include signal transduction inhibitors, interferon inducers, and molecules targeting the interaction between the influenzaNS1A protein and the 30-kD subunit of cleavage and polyadenylation specificity factor.
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