

## “Influenza-2009” - An Escape from Disaster

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### Abstract:

In April 2009, World Health Organization declared the first ever public health emergency affecting overseas countries, territories and communities of the world with a new strain of the influenza A virus causing a global pandemic. This novel strain (H1N1) of the virus appears to be of swine origin and contains a unique combination of gene segments that have not been previously identified in swine or human influenza viruses. The symptoms of the 2009 H1N1 flu virus are clinically similar to those of seasonal influenza and have ranged from mild to severe. The neuraminidase inhibitors provide valuable defences against the virus, but their massive use has led to the development of resistance to these antiviral agents. Vaccination is the only effective way to protect people from contracting illness during epidemics and pandemics of influenza.

### Keywords:

Pandemic, Influenza, H1N1, Flu, Influenza A virus

Forty one years after the last influenza pandemic, while everyone was worrying about the avian influenza A (H5N1) virus causing a pandemic, an apparent new chapter is opened with the emergence of new strain of influenza A virus. On 24<sup>th</sup> April, the World Health Organization (WHO) declared the first ever public health emergency of international concern indicating the occurrence of confirmed human cases of swine influenza in Mexico and United States.<sup>1</sup> Subsequently the Centre for Disease Control and Prevention (CDC) confirmed that these human influenza cases were caused by a novel strain of influenza A virus to which there is little or no population immunity.<sup>2</sup> On June 2009, the WHO rated the pandemic alert from phase 5 to 6, signalling that the first pandemic of the 21<sup>st</sup> century was underway. It was however stressed that the rise in the pandemic alert level was mainly attributed to the global spread of the virus rather than its severity. The pandemic potential of influenza A viruses has been ascribed to their genetic and antigenic instability and their ability to transform by constant genetic re-assortment or mutations, which can result in the emergence of novel progeny subtypes capable of both infecting and leading to sustained person to person transmission.<sup>3</sup> The newly emerged strain contains a combination of gene segments that have not been previously identified in swine or human influenza viruses.<sup>4</sup>

### Historical Perspectives

Influenza has been recognised for hundreds of years, but the cause was unknown for most of this time. Hippocrates had defined this disease about 2400 years ago, but lacked laboratory confirmation.<sup>5</sup> The year 1580, marks the first instance of influenza recorded as an epidemic even though there is possibility that there were many prior influenza epidemics.<sup>6</sup> The word influenza (meaning influence), first used in 1743 originated from the Latin word “Influenza”, named so because

the disease was considered to be caused by unfavourable astrological conditions. Since 1700, there have been approximately a dozen influenza A virus pandemics and the lethal outbreak of 1918-1919 is dubbed as the greatest medical holocaust in recorded history, killing up to 50 million people worldwide.<sup>7</sup>

The earliest evidence of influenza A virus causing acute respiratory illness in pigs was traced to the 1930s. Swine influenza A viruses are antigenically very similar to the 1918 human influenza A virus and they may all have originated from common ancestor.<sup>8</sup> From 1930 to 1990, classic swine influenza A was the commonest swine influenza virus circulating amongst the swine population during which the virus did not undergo much genetic change. Antigenic variants of these classical influenza viruses emerged in 1991 and the real antigenic shift occurred at the ends of last century when the classical swine influenza virus re-assorted with human influenza A virus and a North American lineage avian influenza virus. This resulted in the emergence of multiple subtypes including H1N2 and H3N2. In the past few years, sporadic cases of human infections caused by swine influenza A virus have occurred, mainly due to subtypes. Occupational exposure to swine was the most important risk factor for infection and fortunately all patients recovered without resulting in efficient, sustained human to human transmission.<sup>9</sup>

### Origin of 2009 Strain

The pandemic that began in March 2009, was originally referred to as “swine flu” because laboratory testing showed that many of the genes in this new virus were very similar to influenza viruses that normally occur in pigs (swine) in North America. But further study has shown that this new strain of virus represents a quadruple re-assortment of two swine strains,

one human strain and one avian strain of influenza. The largest proportion of genes come from swine influenza viruses (30.6% from North American swine influenza strains, and 17.5% from Eurasian swine influenza strains), followed by North American avian influenza strains (34.4%) and human influenza strains (17.5%).<sup>10</sup> Analysis of the antigenic and genetic characteristics of the pandemic influenza A virus demonstrated that its gene segments have been circulating for many years, suggesting that lack of surveillance in swine is the reason that this strain had not been recognized previously.<sup>11</sup> This novel strain is antigenically distinct from seasonal influenza A and possesses previously unrecognised molecular determinants that could be responsible for the rapid human to human transmission. Moreover, antigenic drift has occurred amongst different lineages of viruses, therefore, cross protection antibodies against avian, swine and human viruses are not expected to exist. Emerging scientific data support the hypothesis of a natural genesis, with domestic pigs a central role in the generation and maintenance of the virus. Protein homology analysis of more than 400 protein sequences from the new influenza virus as well as other homologous proteins from influenza viruses of the past few seasons also confirmed that this virus has a swine lineage.<sup>1</sup> Phylogenetic analysis has suggested that initial transmission to humans occurred several months before the recognition of the outbreak and multiple genetic ancestry of this influenza A is not indicative of artificial origin.<sup>11</sup>

#### Situation Update

In March 2009, an outbreak of respiratory illness was first noted in Mexico, which was eventually identified as being related to influenza A.<sup>12</sup> The outbreak spread rapidly to the United States, Canada and throughout the world as a result of airline travel.<sup>13</sup> On 11<sup>th</sup> June 2009, the WHO raised its pandemic alert to the highest level i.e. phase 6, indicating widespread community transmission on at least two continents.<sup>14</sup>

Pandemic influenza was the predominant influenza virus circulating in the US, Europe, northern and eastern Africa and in Australia. Activity of the virus has initially peaked and then declined in North America and in parts of western, northern and Eastern Europe, but activity continued to increase in parts of central and southeastern Europe, as well as in central and south Asia. As of 28<sup>th</sup> February 2010, worldwide more than 213 countries and overseas territories or communities have reported laboratory confirmed cases of pandemic influenza 2009, including at least 16455 deaths; a number the WHO acknowledges significantly underreported the actual number.<sup>15</sup> Most of the deaths have been related to respiratory failure resulting from severe pneumonia and acute respiratory distress syndrome.<sup>16</sup>

In India, the number of confirmed cases till March 2010 was 29,953 and a total of 1410 deaths were reported. The rate of infection has been highest among children and young

individuals of <24 years of age. To date, pandemic influenza A infections are uncommon in persons older than 65 years, possibly as a result of pre-existing immunity against antigenically similar influenza viruses that circulated prior to 1957.<sup>17</sup> High rates of morbidity and mortality has been noted among children and young adults with underlying health problems including chronic lung disease, immunosuppressive conditions, cardiac disease, pregnancy, diabetes mellitus and obesity.<sup>18</sup>

#### Transmission and Shedding

Novel virus is contagious and can transmit from human to human in ways similar to other influenza viruses. The main route of transmission between humans is via inhalation of infected respiratory droplets (range in size from 0.08  $\mu\text{m}$  to 0.12  $\mu\text{m}$ ) produced after coughing and sneezing.<sup>19</sup> Transmission via contact with surfaces that have been contaminated with respiratory droplets or by aerosolised small-particle droplets may also occur. In addition to respiratory secretions, all other body fluids (including diarrhoeal stool) should also be considered potentially infectious.

The estimated incubation period is unknown and could range from 1 to 7 days, although the median incubation period in most cases appears to be approximately 2 days.<sup>20</sup> Shedding of the virus begins the day prior to the onset of symptoms and can persist for 5-7 days in immunocompetent individuals. The amount of virus shed is greatest during the first 2-3 days of illness. Persons who continue to be ill, for a period of longer than 7 days after illness onset, should be considered potentially contagious until symptoms have resolved. Longer periods of shedding may occur in children (especially young infants), elderly adults, and patients with chronic illnesses and immunocompromised hosts who might be contagious for longer periods.

#### Clinical Manifestations

According to the CDC, in humans the symptoms of the 2009 "flu" virus are similar to those of influenza and of influenza-like illness in general. The illness with the virus has ranged from mild to severe and symptoms include fever, cough, sore throat, body aches, headache, chills and fatigue, which are usual features of influenza virus. The 2009 outbreak has shown an increase percentage of patients reporting diarrhoea and vomiting.<sup>16</sup> As these symptoms are not specific to swine flu hence a differential diagnosis of probable swine flu requires not only symptoms but also a high likelihood of swine flu due to person's recent history. The CDC advised physicians to consider swine influenza infection in the differential diagnosis of patients with acute febrile respiratory illness who have either been in contact with persons with confirmed swine flu or who were in states that have reported swine flu cases during the 7 days preceding their illness onset.

The overall severity with this 2009 virus has been less than what was observed during the influenza pandemic of 1918-1919. Most patients appear to have uncomplicated, typical influenza-like illness and recovered without requiring any medical treatment. About 70% of people who have been hospitalised have had one or more medical conditions, which include pregnancy, diabetes, heart disease, asthma and kidney disease.<sup>21</sup> The most common cause of death is acute respiratory distress syndrome. The other causes of death are severe pneumonia with multifocal infiltrates (leading to sepsis), high fever (leading to neurological problems), dehydration (from excessive vomiting and diarrhoea) and electrolyte imbalance. Fatalities are more likely in young children (<5 years), elderly (>65 years) and in people with underlying conditions, which include pregnancy, asthma, lung diseases, diabetes, morbid obesity, autoimmune disorders, immunosuppressive therapies, neurological disorders and cardiovascular disease.<sup>22</sup>

### Laboratory Diagnosis

All diagnostic laboratory work on clinical samples from suspected cases of virus infection should be done in a Biosafety Level 2 (BSL-2) Laboratory. Suspected cases of novel infection should have respiratory specimens (nasopharyngeal, nasal or oropharyngeal swab, bronchoalveolar lavage and endotracheal aspirate) collected to test for the 2009 flu virus. Specimens should be placed into sterile viral transport media (VTM) and to be kept at 4°C. Real time reverse transcriptase polymerase chain reaction (RT-PCR) is the recommended sensitive method for the detection of virus, as well as to differentiate between pandemic 2009 and regular seasonal flu.<sup>23</sup> The other rapid influenza diagnostic tests (RIDTs), although provide results within 30 minutes or even less, none of these tests can distinguish between influenza A virus subtypes. Moreover, RIDTs do not provide any information about antiviral drug susceptibility. Isolation of the virus in cell cultures or embryonated eggs is another method for diagnosis of infection, but may not yield timely results for clinical management and negative viral culture does not exclude the influenza A infection.

However, most people with flu symptoms do not need a test for pandemic 2009 flu, specifically because the test results usually do not affect the recommended course of treatment. The CDC recommends testing only for people who are hospitalised with suspected flu and persons having underlying medical conditions and those with weak immune systems.<sup>24</sup> It is also expressed that treatment should not be delayed by waiting for laboratory confirmation of test results, but rather make diagnosis based on clinical and epidemiological backgrounds and start treatment early.

### Treatment

The virus isolates in the 2009 outbreak are found to be resistant to amantidine and rimantidine. The CDC recommends the use

of neuraminidase inhibitors as the drugs of choice for treatment and prevention of 2009 influenza in both children and adults.<sup>25</sup> Tamiflu (oseltamivir phosphate) and Relenza (zanamivir) are the two FDA-approved influenza antiviral drugs and a third neuraminidase inhibitor peramivir is an experimental drug approved for hospitalised patients in cases where the other available methods of treatment are ineffective or unavailable. Antiviral drugs not only make the illness milder but also prevent serious flu complications. However, the majority of people infected with the virus make a full recovery without requiring medical attention or antiviral drugs. Treatment is recommended for patients with confirmed or suspected 2009 influenza who have severe, complicated or progressive illness or who are hospitalised. People who are not from the at-risk group and have persistent or rapidly worsening symptoms should also be treated with antivirals. Therapy should be started as soon as possible, since evidence of benefit is strongest when treatment is started within 48 hours of illness onset.<sup>26</sup> Treatment should not be delayed while awaiting the results of diagnostic testing nor should it be withheld in patients with indications for therapy who present >48 hours after the onset of symptoms. Beside antivirals, supportive care at home or in hospital, focuses on controlling fevers, relieving pain and maintaining fluid balance as well as identifying and treating any secondary infections or other medical problems.

### Major Concern

The neuraminidase inhibitors oseltamivir and zanamivir provide valuable defences and have been used widely for treatment and chemoprophylaxis of 2009 pandemic influenza A. But the recent emergence of resistance to these antiviral drugs is a matter of immediate concern. Influenza A strain resistant to oseltamivir has been reported from a variety of geographical locales and poses a challenge for the management of severely compromised patients.<sup>27</sup> The CDC warned that the indiscriminate use of antiviral medications to prevent and treat influenza could ease the way for drug resistant strains to emerge, which would make the fight against the pandemic much harder. Most of the patients recover spontaneously without any medical attention and use of antiviral medications should be reserved primarily for people hospitalised with pandemic flu and persons, with pre-existing or underlying medical conditions who are at higher risk for influenza-related complications. It has also been emphasised that early treatment once a patient has developed symptoms, rather than chemoprophylaxis, should reduce opportunities for the development of oseltamivir resistance.<sup>26</sup> The degree to which these drugs will remain effective for the treatment of the novel strain of influenza in the coming months is still a question.

### What's next?

The only possible way to combat the situation is large scale immunization. Antiviral drugs are not a substitute for vaccination and are used only as an adjunct to vaccines in the

control of influenza. Vaccines are one of the most effective ways to protect people from contracting illness during epidemics and pandemics of influenza. The seasonal vaccines do not confer any protection against 2009 H1N1; new vaccines have been licensed and are available.<sup>28</sup> The vaccines are available in both live-attenuated and inactivated formulations. Two types of vaccines are approved by the FDA for use in the prevention of 2009 pandemic influenza virus. These are TIV ("flu shot" of trivalent inactivated vaccine) and LAIV (nasal spray of live attenuated vaccine). The inactivated vaccine is contraindicated in patients with severe allergic reaction to eggs or any other component of the vaccine. The live attenuated vaccine is licensed for persons aged 2 through 49 years who are not pregnant, are not immunocompromised and have no underlying medical conditions. Children less than 5 years who have asthma and are taking long term aspirin therapy should also not receive live vaccines. Otherwise, both vaccines are safe and highly immunogenic and a single administration leads to robust immune response in 80% to 90% of adults aged 18-64 years and in 56% to 80% of adults aged 65 years and older with in about 10 days.<sup>29</sup> Children younger than 10 years will require two administrations of the vaccine separated by at least 21 days. Adverse effects following vaccination are minor, just like those of seasonal influenza vaccine and are self limiting. Concerns regarding the risk of Guillain-Barre syndrome (GBS) after vaccination have been raised. Various studies have suggested that the risk of GBS is higher from influenza itself rather than from the vaccine and the other adverse effects.<sup>30</sup> The CDC is now encouraging everyone including people of 65 years and above to get vaccinated against the 2009 strain of influenza.

The Government of India has recently approved a split virus, inactivated, non-adjuvant monovalent vaccine (Panenza by Sanofi Pasteur) to inoculate frontline health workers and those who have a high risk of getting infected.<sup>31</sup> Groups of health care workers has also been singled out by the European council for attention and immunization.<sup>32</sup> Infection control practices in the health care settings should be followed along with as per the guidelines.<sup>33</sup> Patients should also be educated regarding the other preventive measures, including using tissues to cover their mouth and nose when coughing and sneezing, developing good hand washing techniques, use of alcohol based hand-rubs, avoiding contact with ill persons if possible and staying home when ill unless medical attention has been given.

The flu season seems to be dying down in 2010 but the war is yet not over. Lessons must be learnt from the previous influenza pandemics and it is still important to get vaccinated against the flu and be prepared, as activity as well as virulence might increase again in the coming season. The words of Margaret Chan (Director General, WHO) to be remembered that "the virus writes the rule and this one like all influenza viruses can change the rules, without rhyme or reason, at any time".

#### Competing Interests

None declared

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