

## **Etiopathogenesis and Management of Swine Flu (H1N1 Flu) Outbreak**

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### Review Article

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#### **Article History**

*Received: 14.05.2018*

*Accepted: 27.05.2018*

*Published: 30.06.2018*

#### **DOI:**

10.21276/sjams.2018.6.6.9



**Abstract:** Since the pandemic of 2009, the H1N1 virus has broken out in different parts of India causing 6916 deaths from 2009 to 2017 in India. Swine influenza spreads from person to person, either by inhaling the virus or by touching surfaces contaminated with the virus, then touching the mouth or nose. It produces symptoms similar to other flu symptoms. Treatment is largely supportive and symptomatic. Management largely includes the potential use of antiviral agents like oseltamivir or zanamivir. WHO also recommends vaccination of the high-risk group with seasonal influenza vaccine. Since swine flu can directly be transmitted from one person to another through air droplets, people who fail to follow proper hygiene, especially in crowded places and slum areas are at a high risk of contracting the virus. Proper preventive and control measures thus must be ensured. To avoid resistance and complications we should judiciously use antiviral agents as we have limited treatment options. There should be campaign for health education and awareness among citizens by proper Information Education and Communication (IEC) mechanism.

**Keywords:** H1N1, influenza virus, oseltamivir, vaccine, zanamivir, IEC.

### **INTRODUCTION**

The World Health Organization (WHO) had declared the swine flu a pandemic in 2009. The name Swine flu was given because the virus was first isolated in pigs (swine) in 1930 in the United States of America (USA) [1-4]. The swine flu pandemic of 2009 took its origin in Mexico [1-4].

### **Indian scenario of swine flu**

Indian scenario of swine flu outbreak appears to be grim when we looked at the report, 'Seasonal influenza (H1N1) - State/UT-wise, year-wise number of cases and deaths from 2010 to 2017' states that more than one lakh people were infected by H1N1 in the past seven years. In the year 2017 there were 38810 affected cases and 2264 deaths [5].

On examining the report it is evident that there were maximum cases and death in the year 2015. There were just 1786 cases across the country in 2016, the over-all number of cases has increased by more than 20-fold in 2017 as compared to the previous year which may be attributed to better national surveillance

and better laboratory detection systems [6] or might be immunity acquired during previous outbreaks has diminished. Immunity develops either through an infection or by vaccination wanes over time [6] or the circulation of the new swine flu virus, the Michigan strain, in India in 2017 may be the main reason which has contributed to the sharp rise in the cases of viral infection. The increased caseload and mortality in 2017 compared with last year could be because pre-existing immunity developed through exposure to the California strain is now no longer effective, and people are therefore not immune to the new strain [7, 8].

**Annexure-I: Seasonal Influenza (H1N1) – State/UT- wise, Year- wise number of Cases and death from 2011 to 2018 (till 14<sup>th</sup> January, 2018)**

S. No.	States/UTs	2011		2012		2013		2014		2015		2016		2017		2018 (As on 14.01.2018)	
		C	D	C	D	C	D	C	D	C	D	C	D	C	D	C	D
1	Andaman & Nicobar	0	0	0	0	0	0	0	0	4	0	0	0	2	1	0	0
2	Andhra Pradesh	11	1	326	34	71	8	10	5	258	36	12	5	476	14	0	0
3	Arunachal Pradesh	0	0	0	0	0	0	0	0	0	0	0	0	5	1	0	0
4	Assam	0	0	0	0	0	0	0	0	31	4	0	0	199	5	0#	0#
5	Bihar	1	0	0	0	0	0	0	0	352	6	0	0	26	0	0	0
6	Chandigarh	0	0	1	0	37	5	0	0	23	7	6	0	63	6	0	0
7	Chhattisgarh	0	0	10	3	1	1	0	0	239	53	6	4	305	64	0	0
8	Dadra & Nagar Haveli	0	0	0	0	0	0	0	0	26	6	1	0	15	4	0	0
9	Daman & Diu	0	0	0	0	0	0	0	0	5	1	0	0	6	2	0	0
10	Delhi	25	2	78	1	1511	16	38	1	4307	12	193	7	2835	12	8	0
11	Goa	7	0	9	0	0	0	1	1	193	19	6	0	260	12	0	0
12	Gujarat	7	4	101	30	989	196	157	55	7180	517	411	55	7709	431	4	0
13	Haryana	6	4	18	5	450	41	5	0	433	58	68	5	252	9	5	0
14	Himachal Pradesh	14	3	2	2	0	0	0	0	123	27	14	5	77	15	0	0
15	Jammu & Kashmir	13	1	0	0	76	2	0	0	495	20	2	0	139	25	8^^	6^^
16	Jharkhand	0	0	0	0	0	0	0	0	16	6	1	1	35	2	0	0
17	Karnataka	100	12	878	48	122	19	303	33	3565	94	110	0	3260	15	1	0
18	Kerala	210	10	623	14	10	1	62	15	928	76	23	1	1414	76	3	0
19	Lakshadweep	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
20	Madhya Pradesh	9	4	151	26	113	32	17	9	2445	367	38	12	802	146	2	0
21	Maharashtra	26	5	1551	135	643	149	115	43	8583	905	82	26	6144	777	1	0
22	Manipur	0	0	0	0	0	0	0	0	5	2	0	0	8	1	0	0
23	Meghalaya	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
24	Mizoram	0	0	0	0	20	1	0	0	4	0	0	0	0	0	0	0
25	Nagaland	0	0	0	0	0	0	0	0	4	0	0	0	0	0	0	0
26	Odisha	0	0	2	0	0	0	0	0	76	13	1	0	414	54	0	0
27	Pondicherry	1	0	63	2	0	0	0	0	57	4	1	0	168	9	0	0
28	Punjab	46	14	13	4	183	42	27	6	300	61	177	64	295	86	6	2
29	Rajasthan	36	11	343	60	865	165	64	34	6858	472	197	43	3619	279	355	19
30	Sikkim	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
31	Tamil Nadu	34	4	750	40	37	6	58	8	898	29	122	2	3315	17	3	0
32	Telangana*	-	-	-	-	-	-	78	8	2956	100	166	12	2165	21	5	0
33	Tripura	0	0	0	0	0	0	0	0	0	0	0	0	44	0	0	0
34	Uttarakhand	0	0	1	1	24	7	0	0	105	15	20	5	184	22	0	0
35	Uttar Pradesh	57	0	124	0	98	8	2	0	1578	50	122	16	3858	132	1^	0^
36	West Bengal	0	0	0	0	3	0	0	0	544	30	7	2	716	26	0	0
	Cumulative Total	603	75	5044	405	5253	699	937	218	42592	2990	1786	265	38810	2264	402	27

^^ As on 13.01.2018; ^ As on 12.01.2018; # As on 07.01.2018

**Abbreviations: C-Cases, D- Deaths**

\*Telangana State has reporting separately since Nov, 2014 after separation from Andhra Pradesh Disclaimer: The reports on cases and deaths of seasonal influenza (H1N1) are based on the reports received from States/UTs to Central Surveillance Unit, Integrated Disease Surveillance Programme, NCDC, Delhi.

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Etiology-Swine flu is a disease of respiratory system caused by influenza viruses which leads to symptoms like nasal secretions, cough, pyrexia, decreased appetite, and listless behavior [1-4]. The causative virus of the swine influenza is the Influenza A belonging to one of the five subtypes namely: H1N1, H1N2, H2N3, H3N1, and H3N2 and out of these five subtypes, the H1N1 Influenza A strain has been isolated in the infected humans and the rest four subtypes were only exclusive in pigs [4]. The H1N1 virus possess two antigens: H1 (Hemagglutinin type 1) and N1 (Neuraminidase type 1) and it is an enveloped RNA virus of the family orthomyxoviridae[1-4] Swine influenza was first proposed to be a disease related to human flu during the 1918 flu pandemic when pigs became ill concurrently with the humans. However the first identification of an influenza virus to be cause of disease in pigs occurred about 10 years later in 1930. Though direct transmission from pigs to humans is rare but pigs may be reservoir as there might be retention of influenza strains in pigs after these strains have disappeared from the human population which later emerges to reinfect humans once human immunity to these strains has waned [2].

This virus demonstrates all requisite characteristics of a pandemic strain as it is of sufficient virulence to cause human disease, and to a certain degree, humans are immunologically naive to the virus such that exposure can result in a productive infection and it can be passed from human to human[9]. With the infection spreading by sneezing, coughing and close contact and the virus can randomly combine with bird and pig influenza virus to produce new virus strains [10].

#### DISEASE TRANSMISSION

The main modes of transmission of swine flu virus in humans from person to person are inhalation of infected droplets (during sneezing, or cough), direct contact with the infected patient and indirectly by contact with fomites that are contaminated with respiratory or gastrointestinal secretions. The virus can survive over the hard surfaces for about 1-2 days and on porous surface like cloth, tissue, paper for about 8-12 hours [3, 11]. H1N1 swine influenza is a contagious disease and can spread to the household members of the infected person having 8% to 19% chances of getting infection [4]. The 2009 H1N1 pandemic was not a zoonotic disease, but spread from human to human and the virus does not spread by eating cooked pork. However people working with poultry and swine are exclusively at increased risk of zoonotic infection with influenza virus endemic in these animals, and thus constituting a population of human hosts in which zoonosis and reassortment can co-occur [12]. Research revealed that H1N1 swine influenza is same contagious as the usual human influenza [11]. Because droplets do not remain suspended in the air and travel short distances not more

than 6 feet so close contact required for transmission. The potential for fecal viral shedding and subsequent fecal-oral transmission should be also considered and well-investigated as many patients with swine influenza infection had diarrhea. However, susceptibility of ocular, conjunctival, or gastrointestinal infection remains yet unknown [13, 14]. The range of estimated incubation period in humans is 1 to 7 days. The period of infectivity of infected person is one day before the onset of symptoms and up to 7 or more days after becoming symptomatic. However the infectious period may be longer in young children and in immunocompromised or severely ill patients[15].

#### PATHOGENESIS

H1N1 virus exhibits two main surface antigens, H1 (hemagglutinin type 1) and N1 (neuraminidase type1). Out of eight RNA strands of H1N1 one strand had derived from human flu strains, five from swine strains, and two from avian (bird) strains. It causes breathlessness like H5N1 by mechanism of cytokines burst, fluid secretions into organs and break out of infected cells due to neuraminidase and it possesses significant pandemic potential [16].

The molecular markers of pathogenicity are described below-

- 7 PB1F2 coding sequence which is exclusively absent in human influenza viruses. However reassortment event (genes shuffling with other influenza viruses) may lead to the incorporation of a gene responsible for PB1F2 production [17].
- The low degree of identity between the viral hemagglutinin molecules of this strain and other human flu viruses so cross immunity not effective.
- A polybasic cleavage site which is a protease site in the viral hemagglutinin, which plays an important role in the pathogenicity of avian influenza viruses. These host proteases enable virus fusion with a host cell by activating the hemagglutinin molecule [18].

The clinical spectrum of swine influenza infection ranges from self-limited illness to severe outcomes like respiratory failure and death. Secondary complications like primary viral pneumonia, secondary bacterial pneumonia, and exacerbations of underlying chronic conditions may lead to severe illness and deaths associated with seasonal influenza epidemics.

The various pathological changes observed in swine flu patients includes interlobular edema, blood-tinged fibrinous exudates in airways with peribronchial and perivascular cellular infiltration, fibrinous pleuritis, extensive alveolar atelectasis, interstitial pneumonia, and emphysema and enlarged bronchial and mediastinal lymph nodes[19].

### Clinical manifestations

The clinical manifestations of the swine flu are same as any other flu. The symptoms include fever, chills, upper respiratory tract symptoms (cough, rhinorrhea, sore throat, watery eyes, and redness of eyes), headache, malaise, myalgia, arthralgia, dyspnea, tachypnea, vomiting and diarrhea [1]. The immunocompromised patients and the patients of extreme age group (infants and elderly) may present with atypical presentations like altered mental status and respiratory distress [1].

Individuals having high risk of getting a severe infection with swine flu and higher mortality include 12

- Children less than 5 years old
- Old persons (65 years of age and older)
- People with disease conditions like diabetes mellitus, chronic pulmonary diseases (including asthma), congestive heart failure, renal failure, hepatic failure, hematological abnormalities (including sickle cell disease), neurologic or neuromuscular disorders
- Pregnant women.
- Immuno-compromised patients (caused by medications or by HIV)

Severe cases of swine flu may present with the following clinical syndromes 13:

- Diffuse pneumonitis/ rapidly progressive pneumonia associated with severe, refractory hypoxemia (acute respiratory distress syndrome).
- Secondary bacterial pneumonia,
- Worsening of the chronic underlying diseases like congestive heart failure, chronic renal failure, chronic liver disease or end-stage liver disease, poorly controlled diabetes, or immune compromised patients, worsened chronic obstructive pulmonary disease and asthma in those with preexisting disease.
- Bronchiolitis and croup in infants and young children leading to hospitalization

### DISEASE DIAGNOSIS

Physicians should suspect novel influenza a virus if cases presented with an acute febrile respiratory illness or sepsis-like syndrome. Physicians should be highly cautious if the person resides in an affected area even if the illness is mild. If the persons require hospitalization or are at a high risk for severe disease there is indication for investigation. 20, 21 For diagnosis of H1N1 influenza in a patient with suspicion of swine flu we requires collection of upper respiratory tract specimen (nasopharyngeal swab, throat swab, nasal aspirate or nasal washing) best within the first 5 days of onset of illness (the period of infectivity). The sample is then tested by using real time reverse transcriptase polymerase chain reaction (RT-PCR), virus isolation or culture, and assays to

detect a 4-fold rise of influenza virus antigens [12, 22, 23]. Because the other Rapid Antigen Tests available have low sensitivity and specificity so not recommended for diagnosis [4, 12, 23]. The gold standard for diagnosis with high sensitivity and specificity is RT-PCR 23. The sample should be collected by trained physician or microbiologist preferably before start of antiviral treatment and must be kept in a refrigerator (not a freezer) at 4°C in viral transport media until sent for testing and should be sent within 24 h for investigation. A negative result does not exclude a diagnosis of swine influenza A. Though a positive result may be helpful, but it does not distinguish between seasonal and swine influenza viruses as test have not 100% sensitivity and specificity. The various diagnostic tests available are RT PCR, Nucleotide Sequencing, and phylogenetic analysis 24.

### Management

Treatment of influenza is largely symptomatic and includes rest, increased fluid intake, cough suppressants, and antipyretics and analgesics along with isolation to avoid spread. For severe cases we may require intravenous fluid and other supportive measures. Management largely includes the potential use of antivirals for patients presenting with illness due to influenza virus infection. For influenza we have two main classes of anti-viral agents available which are neuraminidase inhibitors (NAIs) (oseltamivir, zanamivir, Peramivir, Laninamivir), and Adamantanes i.e. M2 inhibitors (amantadine and rimantadine). The pandemic H1N1 Influenza A strain (swine flu) has been found to be resistant to adamantanes, so the only choice of treatment are the NAIs [3, 4]. The mechanism of action of NAIs is inhibition of the escape of the virus from the infected cell and therefore controlling the spread of infection [4] We have two drugs Oseltamivir and Zanamivir which are approved and widely used for swine flu. Oseltamivir which is available in the form of oral capsules can be used in patients above one year of age for both treatment and chemoprophylaxis. The Indian government had recommended Oseltamivir as the drug of choice. It is generally well tolerated having some gastrointestinal side effects (nausea, vomiting) with high doses and have less common side effects like anaphylaxis, rashes, vertigo, insomnia and bronchitis 25. Zanamivir is available in the form of dry powder and is administered by inhalational route. Zanamivir is recommended as treatment option for cases above seven years of age and as chemoprophylaxis in patients above five years of age 25.

As per World Health Organization guidelines cases presenting with uncomplicated clinical presentation due to confirmed or strongly suspected virus infection and belong to a group known to be at higher risk of developing severe or complicated illness then should be treated with oseltamivir or zanamivir as

early as possible. However if patients have uncomplicated illness and are not in a higher risk group may not need to be treated with antivirals. If the case present with severe or progressive clinical presentation in all patients including children and adolescents, oseltamivir is given as early as possible and laboratory confirmation of influenza virus infection is not necessary for the initiation of treatment and a negative laboratory test for H1N1 does not exclude the diagnosis in all patients so early, empirical treatment is strongly recommended. If oseltamivir is unavailable zanamivir should be used. Patients presenting with severe or progressive clinical illness and unable to take oral medication may be treated with oseltamivir administered through nasogastric or orogastric tube 26.

Severe immunocompromised patients like those with graft versus host disease, or with hematological malignancies, cancer patients undergoing chemotherapy, HIV patients, having severe immunodeficiency need to be treated with oseltamivir at higher dose as soon as possible and for longer duration 26.

If Influenza viruses are known or suspected to be resistant to oseltamivir then zanamivir must be given as soon as possible 26. For preventing and controlling outbreak of Influenza-A H1N1 virus the revised guidelines by Ministry of Health and Family Welfare, Government of India on categorization of seasonal influenza A H1N1 cases during screening for home isolation, testing, treatment, and hospitalization are discussed below-

#### The patients are categorized as

Category A—Patients having mild fever plus cough/sore throat with or without bodyache, headache, diarrhea, and vomiting .Such patients do not require oseltamivir, not required test for H1N1 and should be treated for the above symptoms but should be monitored for their progress and reassessment done at 24-48 h by the doctor and should confine themselves at home to avoid contact with public and high-risk members in the family.

Category B –if the patient has high-grade fever and severe mild illness but with predisposing risk factors, pregnant women, persons aged 65 years or older, patients with lung diseases, heart disease, liver disease, kidney disease, blood disorders, diabetes, neurological disorders, cancer and HIV/AIDS and patients on long term cortisone therapy. These patients not required tests for H1N1 but should confine themselves at home to avoid contact with public and high-risk members in the family. Broad spectrum antibiotics according to guidelines for community-acquired pneumonia may be prescribed.

Category C – In addition to signs and symptoms of Category A and B if patients present with

(a) breathlessness, chest pain, sputum mixed with blood, drowsiness, fall in blood pressure, bluish discoloration of nails OR (b) Children having ILI who had a severe disease as manifested by the red flag signs (somnia, high and persistent fever, inability to feed well, convulsions, shortness of breath, difficulty in breathing, etc.) OR (c) Patients presents with worsening of underlying chronic conditions .Such patients are categorized in Category C and requires testing, immediate hospitalization, and treatment 27.

Oseltamivir is more effective in reducing mortality if treatment initiated within 48 hours of symptoms onset. However in severely ill patients delayed treatment was still found to be effective. For children of age 14 days to 1 year the dose of oseltamivir should be 3 mg/kg/dose twice daily and for children having age less than 14 days of age the recommended oseltamivir dose is 3 mg/kg/dose once daily. Oseltamivir dose should be reduced for infants not getting regular oral feedings and/or have a concomitant medical condition which is supposed to reduce significantly renal function. Amantadine or rimantadine should be avoided in pregnant women and children aged less than 1 year with uncomplicated illness due to seasonal influenza A (H1N1).

Vaccination WHO recommends vaccination of all the healthcare staff coming in contact with the suspected or confirmed cases of swine flu (physicians, nurses, paramedical, ambulance staff). The injectable vaccine against influenza A/H1N1 is available and has to be taken yearly. The immune response of the body takes about 2-3 weeks to develop after vaccination and till then chemo-prophylaxis can be used. When circulating viruses are well-matched with vaccine viruses then Influenza vaccination is most effective and efficacy of the vaccine may be about 70-80%. If the locally circulating virus is different from vaccine virus then it may not be effective at all. So a vaccine may give a false sense of security. So we should take infection prevention and control practices like the use of personal protective equipment 26.

Earlier in March 2017, the World Health Organisation (WHO) had recommended replacing A patients A/California/7/2009 (which has been in use as a vaccine strain since the 2009 swine flu pandemic) with A/Michigan/45/2015 vaccine to combat the newer strain of the H1N1 virus.

The trivalent vaccines recommended by WHO for use in the 2017-2018 in northern hemisphere influenza season contains the following:

- an A/Michigan/45/2015 (H1N1)pdm09-like virus;
- an A/Hong Kong/4801/2014 (H3N2)-like virus; and
- a B/Brisbane/60/2008-like virus.

It is recommended that quadrivalent vaccines containing two influenza B viruses contain the above three viruses and a B/Phuket/3073/2013-like virus.<sup>28</sup>

Supportive Therapy includes maintaining Circulation, Airway and Breathing, maintaining hydration, electrolyte balance, and nutrition. For patients with tachypnea, dyspnea, respiratory distress and less than 90% oxygen saturation oxygen therapy should be used. Indications for Mechanical Ventilation are severe respiratory failure and failure to achieve oxygen saturation of  $\geq 90\%$ .

For reducing spread of infectious aerosols high-efficiency particulate air (HEPA) filters should be used on expiratory ports of the ventilator circuit/ high flow oxygen masks and for shock vasopressors are recommended.<sup>29</sup> Smoking should be avoided and close watch over lower respiratory tract infection and hypoxia must be kept.

The key to prevent swine flu is to develop novel vaccines against the H1N1 virus. The nasal H1N1 influenza virus vaccine developed is a “live virus” vaccine whereas H1N1 injectable vaccine is a “killed virus” vaccine. H1N1 influenza virus vaccine works by exposing the individual to a small dose of the virus, which helps his body to develop immunity to the disease.<sup>30</sup>

#### PREVENTION AND CONTROL MEASURES

Some preventive measures are-(a) Keeping minimum distance of 6 feet from people suffering from ILI especially during sneezing or coughing

(b) Mouth and nose must be covered with a single use tissue paper during coughing or sneezing, and the tissue paper must be properly disposed in the trash after use.

(c) Using facemask/ N95 respirator if available.

(d) Personnel performing aerosol generating activities (e.g.: Collection of clinical specimens, endotracheal intubation, bronchoscopy, nebulizer treatment) or cardiac, pulmonary resuscitation(CPR) or resuscitation involving emergency intubation should also wear a disposable N95 respirator as N95 respirators seal tightly the user face and protect against small particles.

(e) Develop habit of washing hands with soap and water or alcohol-based hand cleaners frequently after coughing or sneezing and when you take off face cover.

(f) To prevent dehydration drink plenty of water.

(g) For preventing spreading of germs avoid touching eyes, nose or mouth.

(h) Avoid traveling while sick for at least 7 days after you fall sick. Confine to home from work or school if you are sick.

(i) There must be provision of separate well-ventilated space for sick people in the home.

(j) Consult with health care providers to enquire about any need for antiviral medications for prevention of swine flu post contact with an infected person. Immediately contact the doctor in case of any side effects like nausea, vomiting, rash or unusual behavior.

(k) Medications for symptomatic relief of fever and pain must be taken which include acetaminophen or any cough medicine until symptoms improve with doctor advice.

(l) Avoid aspirin in children younger than 18 years.

(m) Patients must be placed in a single-patient room with the door kept closed. An airborne infection isolation room with negative pressure air handling is used, if available. Air exhaustion should be done directly outside or can be re-circulated by a HEPA filter 31, 32.

#### CONCLUSION

The swine flu has emerged as a serious infectious disease all over the world. For mitigating swine flu we have to highly focus on the preventive measures, chemoprophylaxis, vaccination and mass awareness programme through proper Information Education and Communication (IEC). The other matter of worry is the mutations in the virus which may result in resistance to the antiviral treatment. More research work is needed to understand and control the spread of this disease. Better vaccines and shorter production times and timely using them according to temporal distribution of swine flu cases in a region are required to address a severe pandemic.

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