

REVIEW ARTICLE

**INFLUENZA A (H1N1) OUTBREAK AND CHALLENGES
FOR PHARMACOTHERAPY**

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Abstract : Influenza A (H1N1) virus, a genetic reassortment of endemic strain of human, avian flu and swine flu, with an inherent ability to mutate continuously has developed a subtype which is causing present flu in humans. As on 10th May, 2009, twenty nine countries are affected with officially reported 4379 cases with Mexico – 1626 affected (45 deaths), US 2254 affected (02 deaths); Canada 280 (01 deaths) and Costa Rica -8 cases (01 death) respectively. Rest of 15 countries have reported less than 100 officially confirmed cases of H1N1 infection. WHO has already declared Pandemic Alert V on 29th April, 2009. If the present flu achieves equivalent virulence to that of 1918-19 pandemic flu, expected deaths will be 62 million people. Travel advisory, stockpiling of antiviral drugs – Tamiflu & Relenza; vaccine development, activation of business continuity planning for maintenance of essential services etc., are some of the important mitigation approaches, being followed all over the world. WHO has a regional reserve of 10,000 million doses of anti-viral drugs. National Disaster Management Authority (NDMA), Government of India, an apex body for disaster management, in active coordination with Ministry of Health & other stakeholders/service providers is maintaining a constant state of vigil on the present Influenza A (H1N1) outbreak. In collaboration with UNDMT, NDMA has outlined a strategy for Pandemic Preparedness beyond Health in April, 2008. Various non-pharmaceutical interventions like detection, isolation and quarantine are required to contain the situation. Accordingly, stockpiling of 10 million doses of anti viral drugs, surveillance at airports, isolation with strict enforcement of quarantine procedures, sustained supply of respiratory masks & other personal protective equipment; deployment of rapid response teams are some of the activities being undertaken by Indian Government proactively. As situation goes to Phase VI, there will be a shift in strategy from active surveillance, detection and quarantine to

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containment, treatment, prevention of spread of disease and maintenance of business continuity beyond health sectors. The major concern is to utilise this latency period, between phase V and VI, to fill the gaps in state of preparedness. It is also essential to focus on development/procurement of appropriate vaccine to manage the situation arising from any further mutation of the existing causative virus to be resistant against existing anti viral therapies. It is a continued effort which can save many lives around the world and everyone has to play its assigned role effectively.

Key words : pandemic
antigenic recycling

influenza A (H1N1)
antiviral drugs vaccines

INTRODUCTION

Recent outbreak of Influenza A (H1N1) might have originated either in swine and then shifted from swine to humans or due to a super-infection in humans by an unknown variant with variable genetic mix. The pathogen that has seized the world's attention has an official name (swine-origin influenza A H1N1), an acronym (S-OIV), a nickname (swine flu) and an apparent birthplace (Mexico). This early reference as 'Swine Flu' was a misnomer as it has not been firmly established in swines yet. It is caused by viral strain of H1N1 endemic to pigs. Influenza is a simple virus, with just eight genes, but it makes poor copies of itself, leading to constant mutation. In H1N1, the 'H' refers to the hemagglutinin protein, and the 'N' refers to the neuraminidase protein (1). It has a close similarity with H5N1 in terms of causing cytokines burst, fluid secretions into organs leading to state of breathlessness. The neuraminidase genetic segment of the virus provides it an ability to break out of infected cells (2). The underlying fact remains that it possess significant pandemic potential and has reached 29 countries within 20 days of the first reported human casualty from Mexico. Food and Agriculture Organisation (FAO), has confirmed that the virus is not

spreading through food products and there is no threat to food chain (3).

Emergence of reassortant H1N1 subtype – the mutation issue

During the seasonal flu outbreaks in animals, the virus (H3N2) do have limited potential to jump from swine-to-humans, however, human-to-human transmission is generally not observed. The ability of H1 N1 to transfer from human-to-human can be attributed to antigenic recycling leading to evolution of mutant strain. The causative viral strain of Influenza A (H1 N1) has similar surface proteins as that of swine virus, thus, belongs to similar category whether it is able to infect swine or not. The virus had three genera namely Influenza virus A, B and C (1). Among these, B has not been reported in swine. A and C are distinct strains endemic to human and swine. Swine influenza is known to be caused by influenza A subtypes H1N1, H1N2, H3N1, H3N2 and H2N3. In these subtypes, H1N1, H3N2 and H1N2 are circulating throughout the world (4–6). Due to the constant mutation of influenza viruses and their ability to swap genetic material with one another promiscuously — particularly if an animal or person is infected with two strains at the same time — this particular strain looks

partly like another hybrid, or what scientists call a reassortant virus (7).

Learning from past incidences

The analysis of incidence occurred in the past revealed the presence of H1N1 virus since one of the biggest pandemic of 1918–19. It has been reported that a modern pandemic of equivalent virulence to that of 1918-19 would kill 62 million people, with 96% of those deaths in low- and middle-income countries (8). Therefore, even stockpiles of anti viral drugs may restrict the outbreak a little as drug resistant virus may emerge. It has been estimated that even

under the most optimistic calculations, and taking adjuvants into account, today's global vaccine-making capabilities would cover less than 10% of the world's population which will also be influenced by distribution pattern (8). The epidemiology of some of the important outbreaks and problems occurred in management of such pandemics is given in Table I.

Antigenic recycling of H1N1

H1N1 was prevalent in US among swine till 1998 and then H3N2 have also been isolated in August, 1998. Seasonal flu is generally experienced from November to

TABLE I: Epidemiology of some of the important outbreaks and lessons learnt.

<i>Outbreak</i>	<i>Epidemiology</i>	<i>Lessons learnt</i>
1918 Flu pandemic (H1N1)	Around 500 million persons at that time affected and caused around 50 million deaths ; fatality rate: 0.2-0.5% (8).	Genetic mix of variant strain is difficult to manage, R&D efforts coupled with epidemiological findings provide necessary guidance during such pandemics (8)
Hongkong Flu 1968-69	Infected an estimated 500,000 Hong Kong residents, 15% of the population, with a low death rate while in US 38,000 people died. Fatality rate: 0.1% (9)	Strain of H3N2 descended from H2N2 by antigenic shift which has now developed antiviral resistance and present in the recent H1N1 outbreak (9).
1976 US outbreak	Feb, 1976 – small outbreak in Armed forces led to a mass vaccination programme for 40 million people (10)	Effective, however, some immediate deaths after vaccination create secondary panic due to vaccination. The causative factor was Guillain-Barré syndrome, a paralyzing neuromuscular disorder, affecting some people who had received swine flu immunizations. This syndrome is a rare side-effect of influenza vaccines, with an incidence of about one case per million vaccinations (10).
1977–1978 Russian Flu	It infected mostly children and young adults under 23 because a similar strain was prevalent in 1947–57, causing most adults to have substantial immunity (11).	Pre-existing immunity might play a protective role in reducing death toll.
Fujian (H3N2) human flu 2003-04	Fujian bird flu strain of the H5N1 subtypes of the Influenza A virus; affected Taiwan (12).	Reassortment event that caused a minor clade to provide a haemagglutinin gene (12).
2007 Philippine outbreak – Swine Flu (Aug 20, 2007)	10 % mortality in swine flu, however, Hog cholera spreads out enhancing number of affected (13).	Secondary complications needs active surveillance and preventive medical management efforts.

April due to influenza virus, however, generally the mutation in these viruses doesn't result in such lethal strains of higher virulence. In 2004, the virus strain H3N2 with triple reassortants from human (HA, NA, and PB1), swine (NS, NP, and M), and avian (PB2 and PA) lineages have been identified in swine and turkey stocks (14). It could be referred as an unusually mongrelised mix of genetic sequences and indicates its potential to jump within species followed by a number of reassortment events. Eventually, now we are facing the present outbreak caused by influenza A virus subtype H1N1, including a strain endemic in humans and two strains endemic in pigs, as well as an avian influenza. Preliminary genetic characterization found that the hemagglutinin (HA) gene in the causative virus was similar to that of swine flu viruses present in United States pigs since 1999, but the neuraminidase (NA) and matrix protein (M) genes resembled versions present in European swine flu isolates. The origin of this genetic mix is not known, however, presumptions are there that swine might act as a mixing vessel (15). The important news is that molecular analysis revealed that it is the same pathogen which has been observed all over the world which boosts the drug companies to develop vaccines (Fig. 1). Spread of H1N1 viral flu- from 20th April to 10th May, 2009 and global efforts taken by WHO are illustrated in Table II & number of affected persons on day-to-day basis are given in Fig. 2A-B.

Symptoms of H1N1 infection – How generic and how specific ?

The generic symptoms include fever, cough, sore throat, body aches, headache,

chills and fatigue. The 2009 outbreak has shown an increased percentage of patients reporting diarrhoea and vomiting specifically. Influenza viruses bind through hemagglutinin onto sialic acid sugars on the surfaces of epithelial cells; typically in the nose, throat and lungs of mammals and intestines of birds (16). The symptoms are not specific only to Swine infection, thus, differential diagnosis followed by confirmation by laboratory testing of a respiratory sample which could be a simple nose and throat swabs is necessary.

Prevention through other pharmaceutical and non-pharmaceutical interventions

At the level V, the management of H1N1 virus requires continued surveillance, detection and quarantine so that virus remains contained. Commercial vaccination of pigs could be one of the effective mitigation strategies. However, the presence of nonreactive H3N2 SIV variants suggests that current commercial vaccines might not effectively protect pigs from infection with a majority of H3N2 viruses. It indicates the continuous presence of virus in the swine population. Culling could be an alternative choice. The second layer of defence is prevention of swine to human transmission is through maintenance of hygiene like frequent washing of hands with soap and water or with alcohol-based hand sanitizers, especially in case of suspected contact. Any flu like symptoms should be immediately reported to public health authorities and social distancing is an effective non pharmaceutical intervention. The third layer of defence is treatment of infected humans using effective anti-viral drugs and vaccines (17–19). If the situation worsens to level

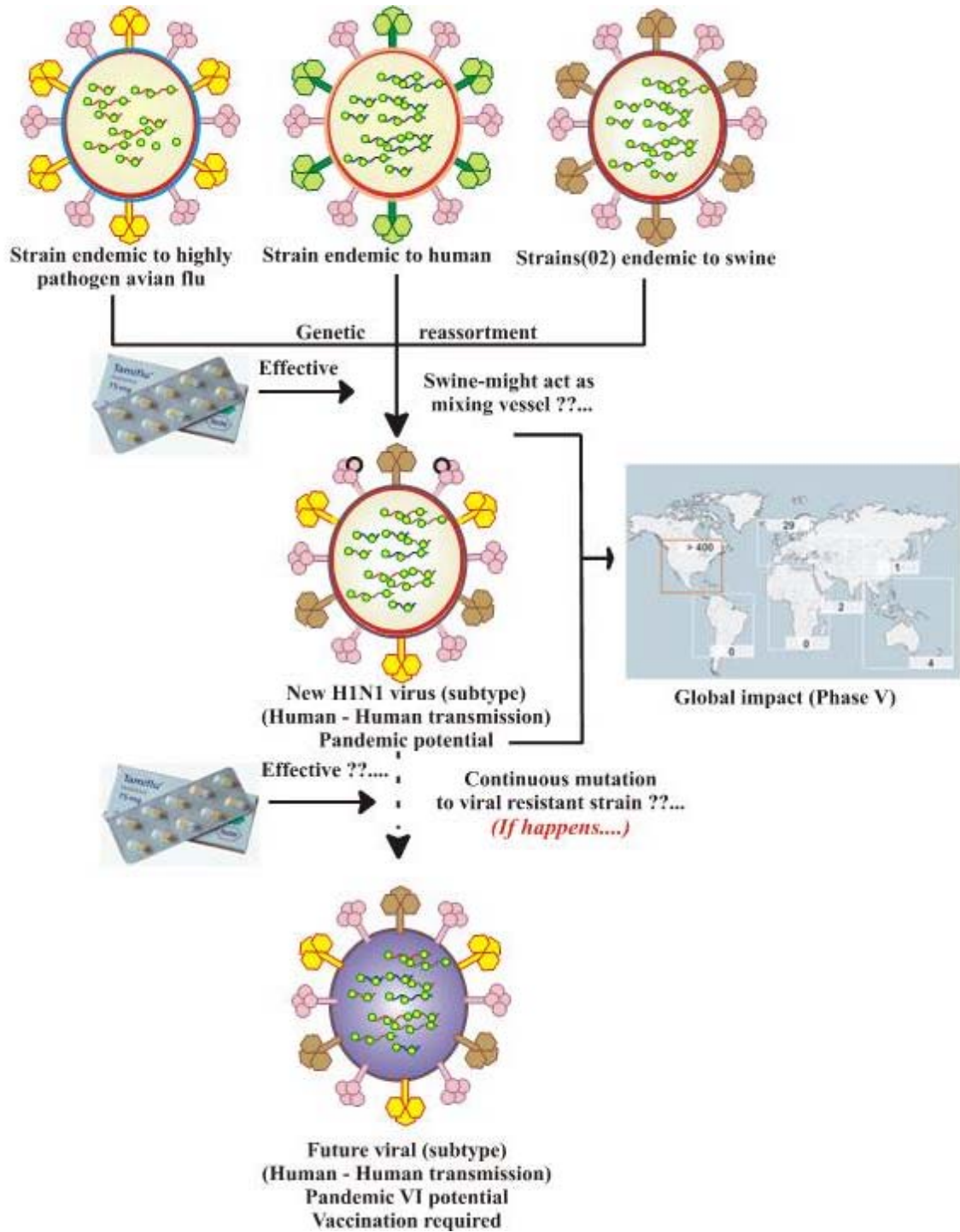


Fig. 1 : Genetic Reassortment of H1N1 leading to Flu outbreak among human population and probable continuous mutation might evolve a viral resistant strain in second pandemic wave (A model based on analysis of various comments available on web and WHO).

TABLE II: Chronology of spread of H1N1 virus in different parts of world.

<i>Date</i>	<i>Existing Status</i>	<i>Preparedness Efforts</i>
20 th April, 2009	First confirmed case has established a new strain of infection and simultaneously, in California, the US Centres for Disease Control and Prevention had identified two children as infected with the same flu strain.	Intensive discussions begin and information exchanged with WHO and other countries
24 th April, 2009	Mexico revealed 59 cases of death due to pneumonia (not confirmed to Swine flu); 24 cases of Influenza like Illness – 03 deaths; 18 Mexican cases confirmed for H1N1 infections; 07 confirmed cases in US (05 in California and 02 in Texas)	National emergency, closing schools, museums, libraries and sports stadiums before shutting down the entire Mexican economy in an effort to contain the epidemic. WHO and PAHO sending expert missions to Mexico to help the medical authorities.
26 th April	US : 20 laboratory confirmed cases: (8 in New York, 7 in California, 2 in Texas, 2 in Kansas and 1 in Ohio- no deaths; Mexico : Suspect clinical cases have been reported in 19 of the country's 32 states.	WHO and GOARN experts are working on the situation; On Saturday, 25 April, upon the advice of the Emergency Committee called under the rules of the International Health Regulations, the Director-General declared this event a Public Health Emergency of International Concern.
27 th April, 2009	Mexico raised the suspected death toll from its outbreak to 149 people — 20 of those confirmed as swine flu — and cancelled all schools until May 6. Nearly 2,000 people there have been hospitalized with serious cases of pneumonia. Canadian government announced six cases of the virus were confirmed in Canada – four in Nova Scotia and two in British Columbia – and that number is expected to rise.	WHO raise the alertness level from III to IV after confirmed human to human transmission.
28 th April, 2009	Influenza outbreak has 192 confirmed cases in Mexico (26 fatalities) and one fatality in Texas in US (64 laboratory confirmed cases). New strain was suspected to have infected more than 2,500 individuals worldwide, with 152 attributed deaths. Five countries have been affected.	WHO maintains the level IV, though suspected to shift to level V and VI soon.
29 th April, 2009	German and Austria added into affected countries; nine countries officially affected with 148 cases; US-91 (01 death); Mexico 26 (07 deaths); Canada (13), New Zealand (03), Britain (05), Spain (04), Israel (02), Germany (03), Austria (01).	WHO raises alert level to V, i.e., transmission confirmed in more than two countries; Travel advisory have been issued for Mexico and affected countries have been given by numerous countries to their citizens.
30 th April, 2009	11 countries affected ; 257 cases : US- 109 (01); Mexico –2500 Mexicans affected, more than 170 died of pneumonia- 97 confirmed cases (07 deaths).	Vigilance at borders is being redoubled; Quarantine of suspected visitors; Heat sensing equipment at airports.

Contd.....

01 st May, 2009	Number of countries affected :13; Total no. of cases affected : 367; Number of deaths Mexico (9/156) and US (1/141).	WHO regional office had a stockpile of 3 million Tamiflu doses; Schools are being closed.
02 nd May, 2009	Number of countries affected : 15; Total no. of cases affected : 615; Number of deaths: Mexico (16/397 cases) and US (1/ 141 cases).	WHO maintains level V pandemic alertness and providing aid and help to different countries.
03 rd May, 2009	Number of countries affected : 18; Total no. of cases affected : 898; Number of deaths: Mexico (19/506 cases) and US (1/226 cases).	WHO admitted the possibility of PHASE VI, though present sustained outbreak is confined to the region of North America, notably Mexico and the United States. Although human cases have also been confirmed in Europe and Asia, there is still no evidence suggesting that sustained community outbreaks have occurred in the two regions. It is the time to be prepared and not just concentrate to wait for next level to rise.
4 th May, 2009	Number of countries affected : 21; Total no. of cases affected : 1085; Number of deaths: Mexico (25/590 cases) and US (1/286 cases).	Travel advisory; Pandemic alert level V; no closure of borders for travel yet.
5 th May, 2009	Number of countries affected : 21; Total no. of cases affected : 1124; Number of deaths: Mexico (25/590 cases) and US (1/286 cases).	Continued surveillance; WHO advises no restriction of regular travel or closure of borders.
6 th may, 2009	Number of countries affected : 22; Total no. of cases affected : 1516; Number of deaths: Mexico (29/822 cases) and US (1/403 cases).	Individuals are advised to wash hands thoroughly with soap and water on a regular basis and should seek medical attention if they develop any symptoms of influenza-like illness especially those which are undergoing International travel.
7 th may. 2009	Number of countries affected : 24; Total no. of cases affected : 2371; Number of deaths: Mexico (42/1112 cases) and US (2/896 cases).	WHO maintains Pandemic Alert Level V.
8 th May, 2009	Number of countries affected : 25; Total no. of cases affected : 2500; Number of deaths: Mexico (44/1204 cases) and US (2/896 cases).	WHO is not recommending travel restrictions related to the outbreak of the influenza A (H1N1) virus.
9 th May, 2009	Number of countries affected : 24; Total no. of cases affected : 3440; Number of deaths: Mexico (45/1364 cases), US (2/1639 cases) and Canada (1/242).	It has been advised that individuals who are ill should delay travel plans and returning travellers who fall ill should seek appropriate medical care.
10 th May, 2009	Number of countries affected : 29; Total no. of cases affected : 4379; Number of deaths: Mexico (45/1626 cases), US (2/2254 cases), Canada (1/280) and Costa Ricia (1/8).	WHO maintains Pandemic Alert Level V.

*Compiled on the basis of WHO 1-240 updates (16) and other various news updates, and web based news (subjected to variation in data due to differences in authenticated information from numerous web based sources).

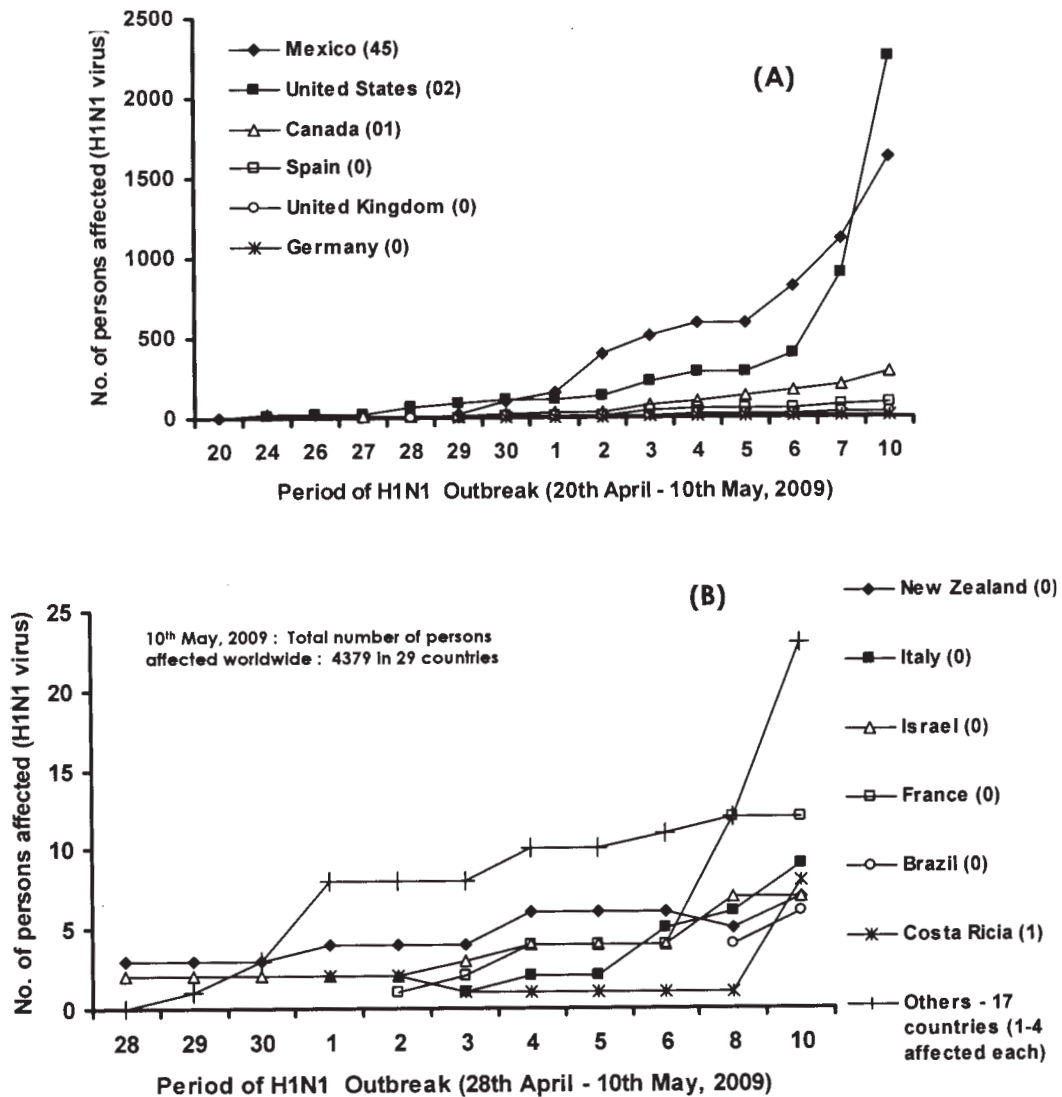


Fig. 2A-B: (A): H1N1 outbreak in maximally affected six countries during first 20 days (20th April- 10th May, 2009); with 45 deaths in Meixco; 02 deaths in US; 01 death in Canada respectively; (B): H1N1 outbreak in six countries (maximal 12 cases; 01 death in Costa Ricia) and other 17 countries (1-4 cases) viz., Austria; Australia, Argentina, El Salvador, China Hong Kong Special Administrative Region; Colombia; Denmark; Guatemala; Ireland; Netherlands; Portugal; Peru, Japan; Poland; Panama; Sweden and; Switzerland with average 1-2 affected cases each.

VI, the mitigation strategy will go for containment, treatment, prevention of further spread and business continuity plans in all sectors.

Current drugs for H1N1 infection

The causative virus H1N1 is responding to neuraminidase inhibitors - oseltamivir and

zanamivir, provided the antiviral therapies are given within first 48 hrs of confirmation of H1N1 in biological samples of the infected individuals.

Oseltamivir (Tamiflu ®) and Zanamivir (Relenza ®)

It is an acetamido cyclohexene that is a structural homolog of sialic acid and inhibits neuraminidase. Its effectiveness in terms of prevention of viral infection especially those who are in close contact of sick persons is 70% to 90% (18–19). These include medical first responders and other emergency functionaries, along with relatives in contact with sick persons. Oseltamivir is a prodrug (usually administered as phosphate), it is hydrolysed hepatically to the active metabolite, the free carboxylate of oseltamivir (GS4071). Like zanamivir, oseltamivir acts as a transition-state analogue inhibitor of influenza neuraminidase. It has biological half life of 3 hrs (20).

Mechanism of action of tamiflu® and relenza®

These neuraminidase inhibitors prevent the virus to escape from the infected cell thereby, preventing the spread of infection and it might lead to possible aggregation and release.

Centre for disease control recommendations

Centre for Disease Control (CDC, USA) recommend Oseltamivir (brand name Tamiflu ®) to both prevent and treat influenza A and B virus infection in people one year of age and older while Zanamivir (brand name Relenza ®) should be used to treat influenza A and B virus infection in people 7 years

and older and to prevent influenza A and B virus infection in people 5 years and older (18). These drugs, their pharmacokinetics, dynamics, toxicology, mechanism of action and side effects are discussed exhaustively by Timpka and co-workers in 2009 (20).

Amantadine and rimantadine confers viral resistance

On the other hand, amantadine (Symmetrel) and a closely related compound Rimantadine (Flumadine) acting *via* interference with a viral protein, M2 (an ion channel) which is required for the viral particle to become “uncoated” once taken inside a cell by endocytosis (2). A total of 193 (92.3%) of 209 influenza A(H3N2) and 2 (25%) of 8 influenza A (H1N1) viruses analyzed contained point mutations resulting in a serine-to-asparagine change at amino acid 31 (S31N) of the M2 protein that conferred amantadine resistance against these viruses (21). These changes prevent the binding of these drugs to the ion channels.

How to handle drug resistance

The mutational behavior of H1N1 is a major future challenge for pharmacotherapy. It has been observed that people use these anti viral drugs even for normal seasonal flu, might develop resistance with time. It is therefore, ensured that drugs should be made available on medical prescriptions only. Another approach is to develop novel vaccines against the H1N1 virus. Government of India has also imposed a complete ban on sale of Tamiflu through retail outlets. It is essential as unnecessary consumption due to panic may results in development of drug resistance.

Vaccine development is a challenging issue

The vaccine for the human seasonal H1N1 flu does not protect against the swine H1N1 flu, as they are antigenically very different. The important underlying factor is that the continuous presence of swine H1N1 flu in human population from varied geographical regions provides enough opportunity to virus to mutate further to become extremely lethal. Thus, a global effort is required to develop newer vaccine to this specific viral strain using antigenic epitopes which are essential for their survival and has least probability to mutate further. If succeeded, the prevention of second wave of such pandemic will be manageable (17). Research efforts are focused on the genetic mix of H1N1 virus to develop a DNA based or other types of vaccines.

On 3rd May, 2009; CDC stated that it had built up a "seed stock" of the virus that could lead to the production of a vaccine, probably takes six months. Though, it will come in batches and has to be rationed. Doctors, nurses, ambulance workers, pharmacists, laboratory technicians and other health workers would get the first shots to prepare them to deal with the sick (18). Other emergency first responders, such as police and fire-fighters, would be next in line before the vaccine is administered to the rest of the population. In India, various orientation and training programmes have been undergone at various states and UTs to have trained doctors and supporting staff to manage any plausible cases of pandemic.

Preparedness and Capacity development for Medical Management of H1N1 in India

India is one of the most vulnerable

countries of Asian subcontinent, that has been affected by Avian flu a number of times especially in Maharashtra, West Bengal and North Eastern states during last three years. So far, the country has managed these incidences effectively by coordinated efforts of Integrated Disease Surveillance Programme (IDSP) run by Ministry of Health and Family Welfare (MoH&FW), Ministry of Agriculture-Department of Animal Husbandry, various laboratories across the country, DRDO and other stakeholders under the advocacy of NDMA. These incidences have been taken as indicators of present pandemic situation. Consequently, MoH&FW developed Pandemic Preparedness Plans to be followed by preparation of plans by other ministries/ Departments concerned. Private sector has also been advised to develop their own contingency plans. The plans should be reviewed and made flexible and stringent enough to manage any such impending situation. Since it is a multi-disciplinary efforts with first line of defence with medical personnel, various inter departmental efforts are required to be taken to synchronize their actions.

Up gradation of BSL Laboratories for confirmed diagnosis of H1N1

After the release of National Disaster Management Guidelines-Management of Biological Disasters, MoH&FW has raised the capacities of National Institute of Virology, Pune to level IV and in network integrated with other laboratories. National Institute of Communicable Diseases (NICD), Delhi; Japanese Leprosy Mission for Asia (JALMA), Agra and NICED, Kolkata are BSL-III laboratories. Additional BSL-III laboratories are being set up at Regional Medical Research

Centre (RMRC), Dibrugarh (Assam); King Institute of Preventive Medicine (KIPM), Chennai (Tamil Nadu). DRDE, Gwalior has also raised their capacity for management of biological warfares. We have significant stockpiles of antiviral to manage such situation (22).

Preparedness for handling impending pandemic

National Disaster Management Authority (NDMA), an apex body for disaster management, has issued Biological Disaster Management Guidelines in July, 2008 with a separate focus on management of pandemics and international cooperation. It has raised and trained four battalions of National Disaster Response Force to manage such situations or man-made disasters. In addition, significant efforts are being taken to sensitize the community about these disastrous situations. While analysis, it has been realised that a stringent mitigation approach with active involvement of non health stakeholders is essential to have a comprehensive management of business continuity should be in place. To achieve this goal, NDMA has initiated a joint effort with United Nations Disaster Management Team, Pandemic Influenza Contingency (PIC) Team, Unit of Office of the Coordination of Human Affairs (OCHA), Geneva; Regional Planning Officer, OCHA Regional Office for Asia Pacific (ROAP). A workshop on 'Pandemic Preparedness beyond Health' was convened on 21–22 April, 2008 with invited experts from all concerned departments and ministries including MoH&FW and representative from WHO. Main focus of the workshop was to define the role of various non-health stakeholders/essential service providers and maintenance of business

continuity during state of pandemic. After two days of intensive deliberations, a document on various regional and national level preparedness efforts to be taken was compiled and released (22). Eventually, the guidelines are made available at ground level for necessary implementation by the concerned stakeholders. A follow up analysis of review of activities around the world was continued till date.

Recent efforts in India after the H1N1 global outbreak

India has not reported any confirmed case of H1N1 infection, though necessary precautionary measures are necessary. Government of India has undertaken efforts for surveillance for large number of passengers identified as having entered India from flu-affected countries like New Zealand, Mexico, the US, Canada, Spain, France and Britain from 27th April till date. 2,000 odd passengers are being traced from Mexico will be traced for any possible symptoms. A large number of medical teams have been deployed at the 12 international airports. Large stockpile capsules of Tamiflu doses and personal protective equipment including triple-layer surgical masks have been dispatched to the regional health offices across the country.

Stockpiling of antiviral drugs

India plans to acquire 10 million doses stockpile as a part of its pandemic preparedness plan. Gilead is the co-developer of Tamiflu, and GlaxoSmithKline controls Relenza have been asked to increase the production of drug. They have 3 millions dosage of Tamiflu on standby with 5 million

doses donated to UN Health agency in 2006 readily deliverable within 24 hrs. To increase its preparedness, Indian Government on 28th April asked companies including Cipla, Ranbaxy, Natco and Hyderabad-based Hetero Drugs to start stocking the chemicals required to produce the drug for the deadly influenza (22). An anticipated target of 10 million doses of antiviral drugs need to be achieved. Cipla has given confirmation to supply 1.5 million doses of generic Tamiflu drugs to help fight outbreak of influenza.

Integrated disease surveillance programme (IDSP)

It is an effective tool with MoH&FW which monitors all the unusual occurrences up to the local region and a rigorous information network to provide information to centre and state authorities. Surveillance measure have been undertaken to get all past information about any visitor visiting India. Separate quarantine areas are being identified at the airports and also issued instructions to follow up the track of people who have visited the affected areas for at least 10 days (23). A continuous surveillance is also required for the immigrants entering the borders through roads, sea and railways from the neighbouring countries.

Detection, isolation and quarantine procedures

Use of clean food and water, municipal corporation department should maintain strict levels of city's hygiene, activation of local house hold based interventions, isolation with strict enforcement of quarantine procedures based on need assessment, R&D efforts to develop vaccines for the new strain of virus, travel checks,

active and even door-to-door surveillance using Integrated Disease Surveillance Programme efforts, activation of Pandemic Preparedness/Response plans and its level of activation are the important efforts that needs to be pursued depending upon the gravity of local situation (19). Detection/identification, laboratory confirmation (non-confirmed, though suspected ones, need to be traced); isolated and then quarantined; immediate reporting to WHO and regional networks, initiate treatment; high alert at source place, necessary containment measures would be undertaken based on risk assessed. Director General of Health Services, Government of India, issued a Special Issue : Human Swine Influenza : A Pandemic Threat in March-April, 2009. NICD, MoH&FW has issued Guidelines for Sample Collection and Handling of Human Clinical samples for Laboratory Diagnosis of H1N1 Influenza & Clinical management Protocol and Infection Control Guidelines-Swine Flu which are available at their website (www.nicd.nic.in).

Community awareness

Awareness about simple precautionary measures for affected victims that should ensure washing of hands regularly and using tissues to cover your mouth and nose while coughing and sneezing. Companies and essential service providers within government, public/private sector should have their contingency plans for necessary implementation. A number of states have initiated the deployment of Rapid Response Teams (RRTs) for management of such situations. As on 10th May, 2009; there are no confirmed cases in India after screening of suspected cases.

Challenges Ahead for Pharmacotherapy

An important lesson learnt from the past is that co-infection of H1N1 swine flu and Oseltamivir (Tamiflu) resistant H1N1 season flu (H3N2 predominates from half a decade) can lead to acquisition of H274Y by the swine flu via recombination or reassortment. It indicates continual evolution with time and might provide resistance as H3N2 has gained resistance increased from 1% in 1994 to 12% in 2003 to 91% in 2005 against standard antiviral drugs like amantadine and rimantadine (24). This virus has an inherent ability to elude the protective antibodies as it constantly changes with time and at any piece of time, human resistance might develop. It is essential to understand that the first wave of such viral pandemics is milder while second wave will be highly lethal. Based on earlier experience of resistance of drug in Norway, France and US in last year H1N1 influenza seasonal spread (not exactly same as of present virus), it could be anticipated that virus may mutate to acquire resistance and then at that time, the alternative could be an effective vaccine (25). Epidemiological findings from past also indicates such possibility. These possibilities pose various challenges to Pharmacotherapy that whether this genetic mix virus due to its inherent nature and an antigenic drift able to mutate further? If yes, whether that mutation enhances the lethality potential with respect to an increase in anti-viral resistance to the current Tamiflu and Relenza? Whether the novel vaccine which is developing against existing H1N1 virus able to manage the virus subtype goes to cause second wave of pandemic as observed in 1918. It is a matter of time that decides the fate of impending pandemic.

Conclusions

To conclude, the level of severity of

Influenza A (H1N1) outbreak indicates that we are at the verge of a 'global tsunami' of flu that has a potential to disrupt all spheres of life around the globe. It is a time where there are a number of confusions in mind related to drug resistance, vaccines and critical issues in comprehensive medical management. While analysis of present status reveals that by 10th May, 2009; we have not reached level VI which means we still have time to make ourselves prepared to mitigate the impact. Phase VI refers to community outbreaks happening in at least three countries in at least two of the WHO's regions. It is also to be kept in mind, even with seasonal flu about half-a-million people die each year from complications and at present, 29 countries has been affected with 4379 cases of infections with 45 deaths (1626 cases of infection in Mexico) and two deaths in US (2254 laboratory confirmed cases) and one death each in Canada and Costa Rica with 280 and 8 laboratory confirmed cases respectively. The number is continuously increasing (with updates available at WHO website (16)). It provides a golden opportunity for countries like India, which are still not affected yet directly, evolve contingencies and fill the gaps to contain the virus within limited spread, preventing its entry into the borders. Efforts undertaken by Indian government in last two years provide significant confidence that we, as a nation, will be able to bounce back from this situation and also be able to extend our helping hands to those countries which are in need of assistance.

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