

Review Article

Pandemic (H1N1) 2009: Epidemiological, clinical and prevention aspects

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ABSTRACT

The influenza pandemic caused by the new H1N1 virus has by now affected all the continents of the world. However, the extent and likely impact are still uncertain. Like seasonal flu, the illness is mild and self-limiting in a great majority of cases, with only 1%–2% of patients requiring hospitalization. In a few cases, the clinical course can deteriorate in a matter of hours, leading to severe complications and eventually death. The risk of complications is higher among those who have pre-existing diseases, such as asthma, heart disease and kidney disease, and among pregnant women. In such cases, antiviral treatment should not be delayed pending laboratory confirmation. The preferred antiviral drug is oseltamivir, and zanamivir is an alternative. Antiviral treatment is not necessary for those who are otherwise healthy, and have mild or uncomplicated illness. It is beneficial for patients with progressive lower respiratory tract disease or pneumonia, and those with underlying medical conditions and pregnant patients. As the supply of antivirals is limited, they should be used judiciously and where appropriate. There is a limited supply of pandemic influenza vaccine available in a few countries and efforts to produce it in India are presently underway. Effective personal preventive measures include shielding one's mouth and nose while coughing and sneezing, frequent washing of hands with soap, avoiding mass gatherings and voluntary isolation by symptomatic individuals. While at present the virus is causing a mild disease, the next wave may be more severe. Hence, enhanced surge capacity of health services is required for the clinical management of an increased patient load.

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INTRODUCTION

Influenza is an old disease caused by influenza virus strains A, B or C. Of these, A is the predominant strain that causes human disease. Influenza viruses are by nature unstable and unpredictable,

and have the unique capability of changing their antigenic characteristics by mutation. In the winter and autumn seasons, they cause frequent outbreaks of acute febrile respiratory illness, usually referred to as seasonal flu. Occasionally, novel strains also emerge, often through re-assortment or exchange of genetic material among influenza viruses from different animal, human or bird sources. Such genetic restructuring occurs regularly in nature and, at times, provides the virus with the capability of causing widespread disease in immunologically naïve populations. The virus can move swiftly across geographical borders to cause pandemics.

Three such pandemics occurred in the previous century, in 1918, 1957 and 1968. The 1918 pandemic was the most devastating, taking a toll of 30–40 million lives worldwide. The subsequent pandemics were relatively milder, each killing around 1 million people.¹ The year 2003 witnessed the appearance of a novel avian influenza A subtype (H5N1), which caused 438 cases and 262 deaths in 15 countries. It remains endemic in poultry populations in many countries, including some countries of the Southeast Asia region, in particular, Indonesia, and occasionally leads to the occurrence of human cases.²

In March 2009, another novel strain of influenza virus A (H1N1), resulting from triple re-assortment, emerged in Mexico and the USA.^{3,4} In late April 2009, the WHO declared that the emergence of this virus represented a 'public health emergency of international concern' and on 11 June 2009, raised the phase of pandemic alert to 6, indicating that a new influenza pandemic was under way.⁵ The H1N1 virus has spread with great speed and ease to all continents and is causing considerable human suffering. It is also having an adverse impact on the health services and the economy.

THE NOVEL VIRUS AND ITS CHARACTERISTICS

The 2009 H1N1 virus contains a combination of gene segments that have previously not been reported in swine or human influenza viruses.⁶ Its genome is the result of a re-assortment of genes from 4 influenza viruses, i.e. North American swine influenza, Asia/Europe swine influenza, human influenza and avian influenza (non-H5) (Table I).⁷ The viruses isolated from humans during the course of this epidemic have been homogeneous, with a difference of a maximum of only 5 amino acids among them. On the basis of current knowledge, there is no known molecular evidence of genetic changes to this virus which would explain its transmissibility among people. Some of the differences between

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TABLE I. Sources of genes in the influenza A (H1N1) virus of 2009

Gene	Source
Polymerase basic 2 (PB2)	Avian influenza virus
Polymerase basic 1 (PB1)	Human influenza A virus
Polymerase acidic (PA)	Avian influenza virus
Haemagglutinin (HA)	Classical swine influenza A virus (triple reassortant swine influenza)
Nucleoprotein (NP)	Classical swine influenza A virus (triple reassortant swine influenza)
Non-structural proteins (NS)	Classical swine influenza A virus (triple reassortant swine influenza)
Neuraminidase (NA)	Swine in Eurasia
Matrix protein (M)	Swine in Eurasia

TABLE II. Characteristics of seasonal and pandemic influenza

Characteristics	Seasonal influenza	Pandemic (H1N1) 2009
Causative agent	Influenza A H1, or H2 or H3 Influenza B	Influenza A H1N1
Seasonal preponderance	Autumn/winter	Summer
Age group at higher risk	Extremes of age	Young adults
Resistance to amantadine	No	Yes
Susceptibility to oseltamivir	Yes (?)	Yes
Natural immunity	May be present	Absent
Availability of specific vaccine	Yes	No
Symptoms pertaining to the GIT	No	25%–50% of cases
Pregnancy a high risk factor	No	Yes

GIT gastrointestinal tract

pandemic influenza H1N1 2009 and seasonal influenza are shown in Table II.

EPIDEMIOLOGICAL ASPECTS

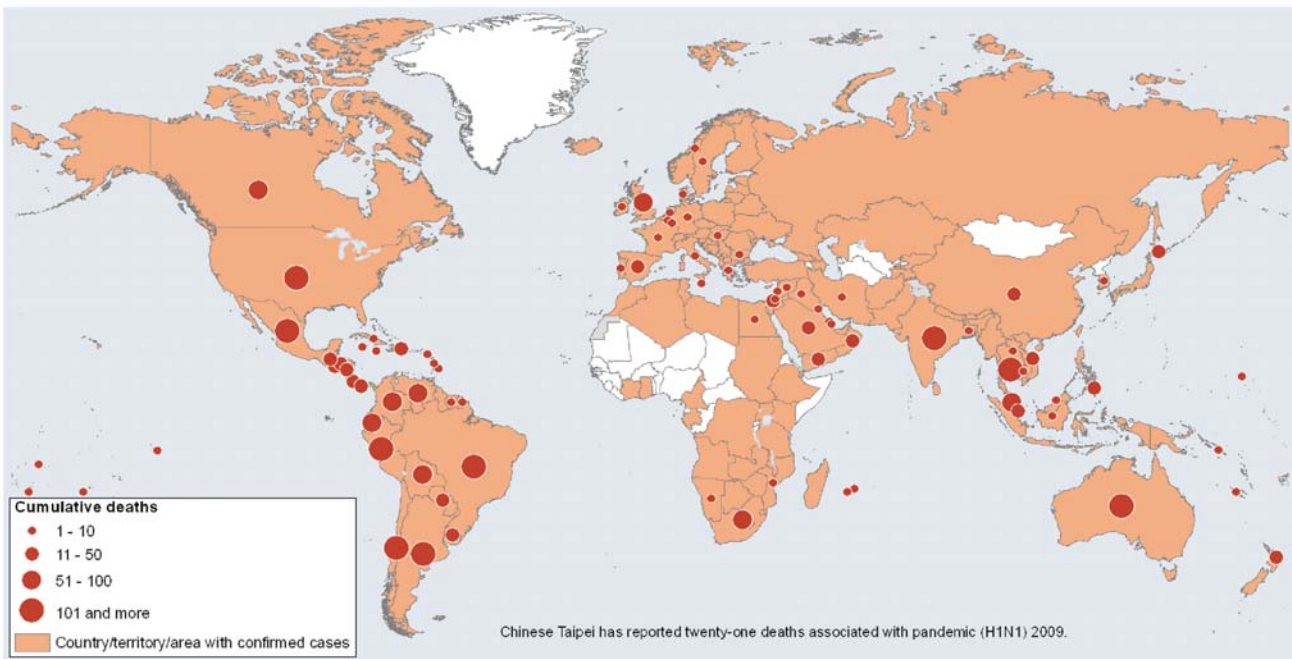
Disease burden

As on 19 October 2009, more than 414 000 cases and about 5000 deaths had been reported to WHO by 195 countries worldwide (Figs 1 and 2).⁸ The actual number of cases would be many more as laboratory facilities for confirmation of the diagnosis are limited. Moreover, many countries no longer test patients with flu-like illness for H1N1.

As of 19 October 2009, in the WHO Southeast Asia region, 10 of 11 member countries have reported 41 513 cases of H1N1 virus infection and 573 deaths. The 3 hardest hit countries in the region are Thailand (26 465 cases, 165 deaths), India (11 068 cases, 351 deaths) and Indonesia (1097 cases, 10 deaths). In India the state of Maharashtra is the worst affected, followed by Karnataka.

It is difficult to estimate precisely the number of people infected by the H1N1 virus as many may not have developed symptoms, while others with mild illness may not have sought medical care. Uncertainties remain about the extent to which this virus may eventually spread. This will, we believe, depend on 3 factors: communicability of the virus, as measured by attack rates; its virulence or severity, as measured by case fatality rates; and the implementation of an effective national response, in particular, proper case management, measured by the surge capacity of the health or medical services.

Pandemic (H1N1) 2009 Status as of 11 October 2009 Countries, territories and areas with lab confirmed cases and number of deaths as reported to WHO



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization
Map Production: Public Health Information and Geographic Information Systems (GIS)
World Health Organization

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Map produced: 14 October 2009 12:18 GMT

Fig 1. Countries, territories and areas with laboratory-confirmed cases of H1N1 and number of deaths as reported to WHO (11 October 2009)

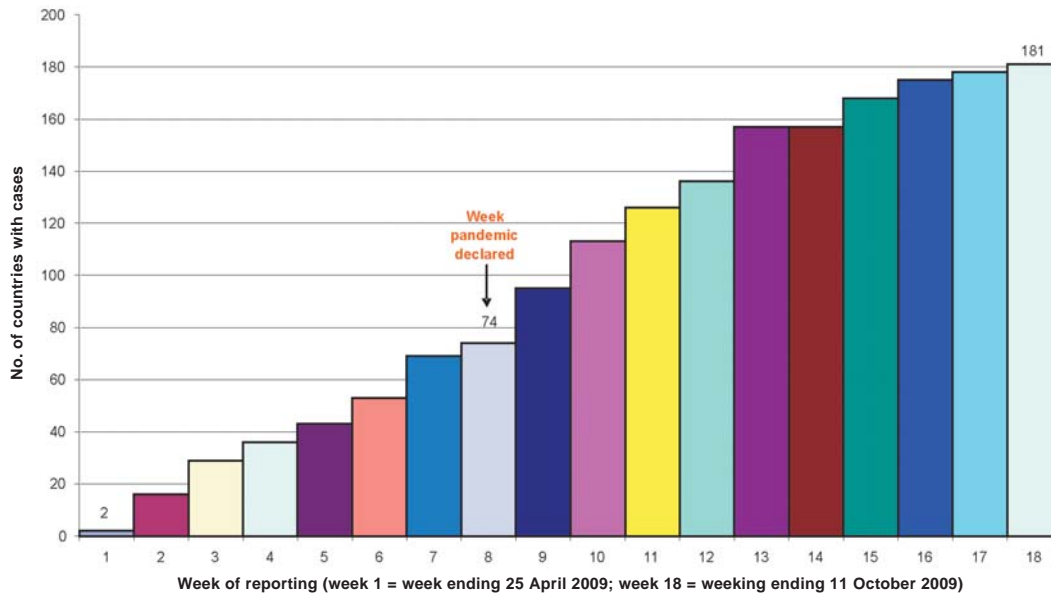


FIG 2. Number of countries worldwide reporting new pandemic H1N1 2009 cases by week

In Europe, the estimated attack rates are in the range of 20%–30%.⁹ In Australia and New Zealand, where the regular flu season is coming to an end, an attack rate of 20% has been assumed. With regard to severity, the disease is labelled as mild to moderate, as in most cases, the virus causes a mild and self-limiting illness, with 1%–2% of the cases requiring hospitalization. The case fatality rates in the USA and the UK have been in the range of 0.3%–0.4%. Taking into account cases that may not have reported to healthcare facilities, the case fatality rate could possibly be in the range of 0.1%–0.2%.¹⁰

In the past 5 months, surveillance data from many affected countries such as Mexico, the USA, the UK, Thailand and India, have provided good indicators not only of the clinical pattern, severity of disease and modes of transmission, but also of how fast and how far the virus can travel in a short period of time. At the macro level, modelling can estimate the likely impact of the pandemic once key parameters such as the basic reproduction rate (average number of secondary cases generated by one case at the start of an epidemic), the time interval between cases and the risks to and severity of the disease among various population groups, become available.^{10,11}

Risk factors

Analysis of the first 8787 cases reported in India shows that the disease has occurred in every age group, indicating that the population does not have immunity to this virus (Fig. 3). In the USA and the UK, attack rates among the elderly have been lower, indicating some exposure to the virus in the past. The risk of complications has been higher among those with pre-existing diseases such as asthma, heart disease and kidney disease, and among pregnant women. In the USA and the UK, obesity has been identified as a risk factor for severe disease.¹²

Transmission

Like seasonal flu, the mode of transmission is through droplets from coughing or sneezing, and through direct or indirect contact with the respiratory secretions of an infected person. There is a risk that people may also acquire infection by touching something

that is contaminated by the virus and then touching their nose or mouth. Food is not yet known to be a vehicle for the transmission of this new influenza virus. Rapid spread among the population has been observed, especially in crowded places such as schools. In school outbreaks in the UK, around 30%–50% of students have been affected. In the USA, the attack rate in schools has been lower, at around 20%. The secondary attack rate in households has consistently ranged from 18% to 30% in countries where data are available.¹⁰

An infected person is infectious from a day before the onset of the symptoms till about 24 hours after the symptoms have subsided. The incubation period is 1–7 days. The basic reproduction rate may lie between 1.2 and 1.7, though a higher figure (2.3) has been reported in closed communities such as schools in Japan. The average generation time, i.e. the mean delay between the time of infection of the index case and the time of infection of secondary cases, irrespective of the setting, is 2.5–3 days.¹⁰

CLINICAL PRESENTATION, DIAGNOSIS AND TREATMENT

Clinical presentation

The data available indicate that the clinical spectrum of infection with the H1N1 virus is broad, and ranges from mild upper

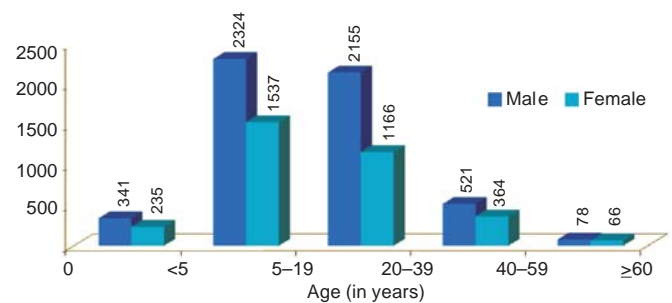


FIG 3. Age and sex distribution of laboratory confirmed pandemic (H1N1) cases (n=8787) in India (data unavailable for 836 cases)

respiratory tract illness to severe complications such as pneumonia resulting in respiratory failure, acute respiratory distress syndrome (ARDS), multi-organ failure and death.⁹

Like seasonal flu, a great majority of cases have fever, cough, sore throat and a runny nose. Gastrointestinal symptoms such as diarrhoea have been reported in 20%–50% of patients, and do not require hospitalization.¹² What is critically important, however, is that in a small proportion of patients, the clinical course tends to deteriorate rapidly, leading to complications and death.^{12,13} Such patients require immediate hospitalization and treatment with antivirals without delay; most deaths during influenza outbreaks have been associated with delayed administration of antivirals.¹⁴ In some countries, the main reason for hospitalization is primary viral pneumonia or viral pneumonitis. Among fatal cases, microbiological evidence of a secondary bacterial or fungal infection has been observed. In the USA, >70% of hospitalized patients and approximately 80% of fatal cases have had underlying conditions considered to put them at high risk for complications.

Laboratory diagnosis

Currently, confirmatory diagnostic tests can be done by specialized laboratories in many countries. Reverse-transcriptase polymerase chain reaction (RT-PCR) provides the most timely and sensitive evidence of infection.¹⁵ Clinical diagnosis (based on acute onset of fever and cough) can be increasingly predictive of infection as the prevalence of infection increases.

At present, there is no validated rapid bedside diagnostic test (including so-called 'point-of-care' diagnostic tests). Commercially available rapid tests for seasonal influenza have uncertain sensitivity (between 10% and 60%) and lack specificity. Both positive and negative results from such tests should be interpreted with caution.

Samples for laboratory tests should be taken from the deep nasal passages, nasopharynx, throat or, if available, bronchial aspirate. Upper respiratory tract sampling using a combination of a nasal or nasopharyngeal swab and a throat swab is advised and may facilitate detection of the virus. It is not yet known which clinical specimen gives the best diagnostic yield for this infection. Appropriate precautions should be taken during specimen collection so that the collector is not exposed to respiratory secretions from patients.

Laboratory tests for initial patients are important in countries which are still free from this disease or have only a few imported cases, and confirmation of community transmission is necessary for specific public health actions. Though laboratory confirmation of H1N1 infection has important implications for case management, antiviral treatment and avoiding the inappropriate use of antibiotics, clinical management (including antiviral treatment) must not be delayed pending laboratory confirmation. In countries where the presence of H1N1 has already been demonstrated, there seems to be no rationale for testing every patient with flu-like illness for H1N1. The tests are expensive and cost between Rs 5000 and Rs 10 000, and it takes time for the results to become available. Many countries such as the USA and the UK, no longer conduct laboratory tests on patients with flu-like symptoms, nor are such cases being reported routinely. As a public health support function in countries with sustained community transmission of H1N1, laboratory services should be utilized to monitor susceptibility of the virus to oseltamivir and any changes in its genetic structure that may indicate enhanced virulence or infectivity.

Case management and antiviral treatment

To date, most human cases of H1N1 infection have had an uncomplicated illness of limited duration. Hospitalization or antiviral therapy is, therefore, not likely to be required for most patients. Supportive care includes antipyretics such as paracetamol or acetaminophen, for fever or pain, and fluids, as needed.

The specific factors that predict an increased risk for progressive disease are incompletely understood. Clinicians and caregivers should watch for signs of possible clinical deterioration (for example, difficulty in breathing, chest pain, coughing up coloured sputum, altered level of consciousness and confusion) and refer such patients immediately to hospital. Clinicians should also take into account any underlying co-morbid conditions (such as immune-compromising conditions, pre-existing chronic lung or cardiovascular disease and diabetes).

Pregnant women are known to be at increased risk for complications of seasonal, avian H5N1 and pandemic influenza infection. Several pregnant women infected with the new H1N1 virus have reportedly been hospitalized and, in many cases, the outcome has been fatal. In a study conducted during the initial phase of the pandemic in the USA, higher hospitalization rates were observed among pregnant women.¹⁶ Six of 11 pregnant women who were admitted died due to pneumonia, followed by ARDS. Consequently, pregnant women with suspected or confirmed H1N1 infection warrant closer observation and, in accordance with national policies, treatment with antivirals.

The virus is currently susceptible to neuraminase inhibitors (oseltamivir and zanamivir), but resistant to M2-inhibitors (amantadine and rimantadine). Oseltamivir is believed to reduce the severity and duration of the illness, and might contribute to preventing its progression to severe disease and death. Important pharmacological differences need to be considered when choosing the neuraminase inhibitor to be given for treatment. Oseltamivir is administered orally and gives a higher systemic level. Zanamivir is to be orally inhaled and is poorly absorbed. Oseltamivir is the recommended treatment for lower respiratory tract complications.

Antiviral therapy may be beneficial especially for pregnant patients, patients with progressive lower respiratory tract disease or pneumonia, and those with underlying medical conditions. WHO recommends the use of antivirals for the treatment of severe or complicated illness. Antiviral treatment should ideally be started early for all patients (including pregnant women and neonates), but it may be used at any stage of active disease when ongoing viral replication is anticipated or documented. It is possible that the virus may replicate for a prolonged period of time in some cases due to a lack of pre-existing protective immunity. The preferred drug is oseltamivir, and zanamivir is an alternative. Patients who belong to a group which is at risk and who have mild or uncomplicated illness may be treated with oseltamivir or zanamivir. If virus activity has been detected in the community, antiviral treatment should not be delayed, especially in the case of patients with pneumonia or progressive lower respiratory tract symptoms. Empirical antiviral treatment with oseltamivir or zanamivir should be initiated as soon as possible after any suspected patient of pandemic influenza has been admitted to the hospital. Treatment is not necessary for those who are otherwise healthy, and have mild or uncomplicated illness.¹⁷

Rare neuropsychiatric symptoms, such as confusion or abnormal behaviour, have been observed after the initiation of treatment with oseltamivir, particularly in children and adolescents, but the contribution of oseltamivir to these events is unknown. Inhaled zanamivir has been temporally associated with broncho-

spasm, and patients with pre-existing airway disease appear to be at increased risk for this severe adverse reaction. Any suspected adverse events should be reported to the national regulatory authorities.

Corticosteroids should not be used routinely to treat patients with H1N1 virus infection. Low doses may be considered for patients with septic shock who require vasopressors and have suspected adrenal insufficiency. Prolonged use can result in serious adverse events, including opportunistic infections and possible prolonged viral replication.

Close monitoring of the genetic character of the virus, including studies for the determination of resistance to oseltamivir, is being done in the global network of influenza laboratories. Resistance to oseltamivir has been identified in a small number of isolated cases associated with post-exposure prophylaxis. So far, only 12 virus isolates have been shown to be resistant to oseltamivir.⁸ None of these isolates has been responsible for the onward transmission of resistant isolates and their occurrence is sporadic. This does not call for any change in the recommendations regarding the use of oseltamivir for the purpose of case management. Surveillance for drug resistance in the context of H1N1 remains a high priority.

PREVENTIVE MEASURES

From a public health standpoint, for a vast majority of populations in developing and resource-constrained countries, pharmacological interventions such as vaccines and antivirals are not likely to play a major role at present, due in part to limited supply, lack of access and the high costs involved. Such countries will have to depend on various non-pharmaceutical interventions.

Non-pharmacological interventions

Non-pharmacological or simple public health interventions include the use of personal protective measures such as shielding one's mouth and nose while coughing or sneezing, frequently washing one's hands with soap, avoiding mass gatherings and voluntary isolation by symptomatic individuals. A full understanding of the risks involved, what precautions to take and whom to consult when one has symptoms is critical. The media plays an important role in communicating risks/targeted messages to the general population. Some of the measures such as the mandatory isolation of cases or quarantine of close contacts, have not been successful in containing the virus. They could even be counterproductive in controlling the outbreak as those who are symptomatic may go underground, or such measures can lead to a false sense of complacency among the general population.

Personal hygiene, including hand hygiene, if observed properly, can be effective in preventing respiratory viral infections, as shown by empirical studies.^{18,19} Media strategies should aim at advising people to observe the basic rules of hygiene. Interventions for social distancing, such as the cancellation of social events and closure of cinemas and schools, may not be effective, and could create social disruption and panic in the community. In Japan, though such an intervention was effective in controlling an outbreak of the infection in a school, social distancing did not seem to have any effect on transmission in the community.⁸ Screening at the port of entry could not prevent entry of the virus in India, Thailand and several other countries. Hence, these measures can be considered only in specific situations.

Healthcare workers have acquired H1N1 in occupational settings.²⁰ Laboratories that process clinical samples should have adequate biosafety facilities (enhanced BSL2). Personal protective

equipment (such as N95 respirators) should be used while carrying out procedures on patients, who should be kept in isolation.

Pharmacological measures

Currently, vaccine is starting to become available in a few countries. Antivirals are also available in limited supply, and should be used judiciously and where appropriate.

Chemoprophylaxis. If the likelihood of complications is low, antiviral chemoprophylaxis should not be offered to individuals at risk for infection or to healthcare workers. If the likelihood of complications is high (either due to the strain or baseline risk of the exposed group), oseltamivir or zanamivir may be used as post-exposure chemoprophylaxis for affected individuals, especially healthcare workers.¹⁷

Vaccination. Vaccine against the H1N1 virus is presently available in a few countries. WHO and its partners, both in the public and private sectors, are working to produce a vaccine against the pandemic virus as early as possible in developing countries too. Substantial progress has already been made and commercial production is about to commence. However, the capacity to produce the vaccine is limited in developing countries. In India, five manufacturers are striving to have this vaccine in the market, but given the technological and regulatory requirements, limited doses of the vaccine are likely to be available only a few months later.

Three objectives that countries could adopt as part of their vaccination strategy include:²¹ (i) protecting the integrity of the healthcare system and the country's critical infrastructure; (ii) reducing the morbidity and mortality; and (iii) reducing transmission of the virus within communities.

The first priority of all countries should be to immunize their healthcare workers (1%–2% of the world's population) in order to protect the essential health infrastructure. Significant pandemic-related morbidity in such workers will compromise the capacity of the health services to care for patients. Despite low rates of hospitalization and case fatality, as the virus invades new territories, the number of people infected, as well as of those developing disease, requiring hospitalization and succumbing to the illness will be many times more than is the case with seasonal flu, thereby stretching the local health services.

The next priority should be pregnant women (2% of the world's population), who appear to be at increased risk for severe disease, especially during the second and third trimesters of pregnancy. Inactivated non-adjuvant vaccines similar to most seasonal influenza vaccines are considered the preferred option, given the extensive safety data on their use in pregnant women. Next in priority could be persons who are above the age of 6 months and have one of several chronic underlying medical conditions, in order to reduce morbidity and mortality. Next in order of priority could come healthy young adults (above 15 years of age to below 49 years of age).

LESSONS FROM PAST PANDEMICS

Since the sixteenth century, influenza has been the cause of several epidemics and pandemics. As each pandemic strain is unique, it is difficult at this stage to make an accurate prediction either of the severity or the overall impact of the current pandemic. The influenza pandemics of 1918 and 1957 both began as mild, but the subsequent waves were more severe. Whether the current one, which is considered mild or moderate in severity, will be more severe during the second wave remains to be seen. However, this is something that the policy-makers and health authorities must consider seriously as a part of the national preparedness and

response to the ongoing pandemic. There are data to suggest that non-pharmacological interventions were useful in preventing deaths during the 1918 epidemic in those parts of the USA where they were implemented.²² However, one must consider how far it would be feasible to effectively implement such interventions in the present context, as also how far they would be acceptable to the population.²³ It is, therefore, reasonable to assume that the overall impact of the pandemic in the twenty-first century could be determined by factors such as the availability of antiviral agents, potential for vaccine development, and modern communication technology to spread prevention and control messages, each of which can possibly attenuate the effect of this pandemic on human life and the world economy.

CONCLUSIONS

The 2009 influenza pandemic has affected most countries of the world within a short span of time. Though at present, the pattern of illness does not differ from that of seasonal influenza, the sheer volume of cases that is expected to occur could easily overstretch the already fragile and overburdened health services, and cause considerable suffering in human populations around the world. It is a matter of much concern that while the novel virus is at present causing a mild disease in most cases, the next wave may be more severe. Larger numbers of severely ill patients requiring intensive care are likely to be the most urgent burden on health services, creating pressures that could overwhelm intensive care units and possibly disrupt the provision of care for other diseases. This calls for an enhanced surge capacity of health or medical services in each country to enable the health facilities to clinically manage an increased patient load in the future and keep the rate of fatality low.

Although, the role of antivirals and vaccines is indisputable, the limited supply and lack of access in most developing countries can undermine the response capacity of the region and hence, enhance these countries' vulnerability in an emergency situation. Traditional non-pharmacological approaches to the prevention and control of disease have stood the test of time. Modern communication tools, the enhanced availability of antivirals and community awareness regarding the desirable behavioural changes may attenuate the effects of this pandemic. As new information about the virus and/or technologies (such as for a vaccine) become available, the opportunity should be taken to further strengthen prevention and control strategies, and minimize the overall health, social and economic effects of the pandemic in the coming years.

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