CDAlert

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Directorate General of Health Services, Government of India

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PANDEMIC INFLUENZA

INTRODUCTION

Influenza pandemics are caused by new influenza viruses that have recently adapted to humans and resemble major natural disasters both in terms of recurrence and magnitude.

The influenza virus, circulating as a pathogen in the human population since at least the sixteenth century is notable for its unique ability to cause recurrent epidemics and global pandemics. Genetic re-assortments in the virus cause fast and unpredictable antigenic changes in important immune targets leading to recurrent epidemics of febrile respiratory disease every 1 to 3 years. This has consistently necessitated the development of new vaccines.

Each century has seen some pandemics rapidly progressing to all parts of the world due to emergence of a novel virus to which the overall population holds no immunity.

The outbreak of H5N1 influenza among birds in recent years (with occasional transmission to human beings) is of major concern because of similarities between the H5N1 virus and the 1918 influenza strain. If H5N1 acquires the capability of human-to-human transmission, it can cause up to several million deaths globally. However, it is not necessary that H5N1 be the causative strain of the next pandemic; it may be caused by a totally new strain.

The present situation is categorized as phase 3: a virus new to humans is causing infections, but does not spread easily from one person to another.

EPIDEMIOLOGY

Influenza is a serious respiratory illness which can be debilitating and may cause complications that lead to hospitalization and death, especially in the elderly.

Influenza viruses belong to Orthomyxoviridae family and are classified into three types A, B or C based on antigenic differences of their nucleo- and matrix proteins. Avian influenza viruses (AIV) belong to type A influenza virus. Epidemics are primarily caused by type A viruses and occasionally by type B viruses. Type C influenza virus has been associated with sporadic cases and minor localized outbreaks.

New epidemic influenza A strains arise every 1 to 2 years by the introduction of selected point mutations within two surface glycoproteins: haemagglutinin (HA) and neuraminidase (NA). The new variants are able to elude human host defenses and there is, therefore, no lasting immunity against the virus, neither after natural infection nor following vaccination. These permanent and usually small changes in the antigenicity of influenza A viruses are termed "antigenic drift" and are the basis for the regular occurrence of influenza epidemics. The major changes in the antigenicity of an influenza virus as shown in table-1, are called "antigenic shift".

Pandemics are rare events that occur every 10 to 50 years. They have been documented since the 16th century and in the last 400 years, at least 31 pandemics have been recorded. During the twentieth century, three influenza pandemics occurred (Table-1).

Table 1: Antigenic Shifts and Pandemics			
	Designation	**Resulting Pandemic**	**Death Toll**
1892	H3N2	Moderate	Not available
1918	H1N1 ("Spanish")	Devastating	50-100 million
1957	H2N2 ("Asian")	Moderate	1-4 million
1968	H3N2 ("Hong Kong")	Mild	1-4 million

Characteristics of influenza pandemics:

- Occurrence outside the usual season
- Extremely rapid transmission with concurrent outbreaks throughout the globe
- High attack rates in all age groups with high mortality rates even in young adults.

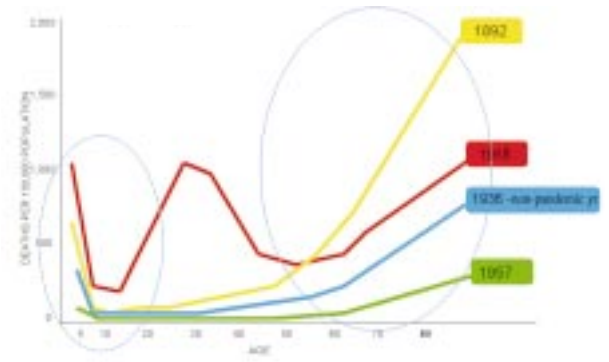

Fig.1: Age specific mortality during past influenza pandemics

Influenza pandemics affect the globe in successive waves; the new viral strain will eventually reach everywhere, and will infect practically every human being within a period of few years. Seasonal excess mortality rates due to pneumonia and influenza may remain elevated for many years after the pandemic has receded.

Fig.2: Emergency hospital during influenza pandemic 1918, Camp Funston, Kansas

The H5N1 strain isolated from fatal human cases in Vietnam has been partially sequenced. All the genes are of avian origin, indicating that the virus has not yet acquired genes from the human influenza virus. The acquisition of such genes increases the likelihood that a virus of avian origin can be readily transmitted from person to person.

At present, H5N1 avian influenza remains largely a disease of birds. The species barrier is significant: despite the infection of tens of millions of poultry over large geographical areas for more than two years, fewer than 300 human cases have been confirmed by a laboratory. Very limited human-to-human transmission of the H5N1 strain was documented in healthcare workers and family contacts.

CAUSATIVE AGENT

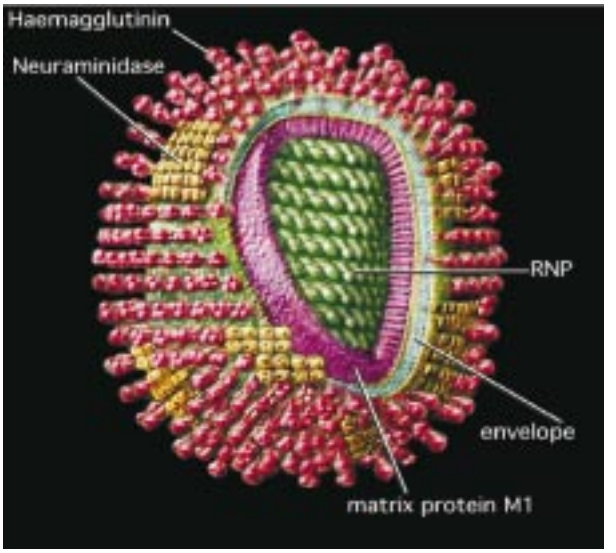

Fig.3: Schematic Representation of Influenza virus.

Influenza A and B viruses are enveloped viruses with a segmented genome made of eight single-stranded negative RNA segments of 890 to 2,341 nucleotides each. They are associated with protein (RNP) and are spherical or filamentous in structure, ranging from 80 to 120 nm in diameter

On the basis of the antigenicity of the surface glycoproteins, haemagglutinin (HA) and neuraminidase (NA), influenza A viruses are further divided into sixteen H (H1-H16) and nine N (N1-N9) subtypes. HA is the major antigen for neutralising antibodies, and is involved in the binding of the virus to host cell receptors. NA is

concerned with the release of progeny virions from the cell surface. **Currently, only viruses of the H1N1 and H3N2 subtypes are circulating among humans.**

The virus is killed by heat (56°C for 3 hrs or 60°C for 30 minutes) and with common disinfectants, such as formalin and iodine compounds.

Table 2: Survival of the influenza virus

	Temperature	Survival Time
Contaminated manure	Cool	3 months
Water	22° C	4 days
	0° C	30 days

In frozen material, the virus probably survives indefinitely. Recent studies indicate that the H5N1 viruses isolated in 2004 have become more stable, surviving at 37°C for 6 days - isolates from the 1997 outbreak survived just 2 days (Table-2).

MODE OF TRANSMISSION

Human-to-human transmission

The influenza virus enters the body through the nose or throat. It then takes between one to four days for the person to develop symptoms. Someone suffering from influenza can be infectious from the day before they develop symptoms upto five to seven days afterwards. Children can spread the virus for 10 days or longer.

Influenza is transmitted from person to person via:

- Droplets (> 5 µm in diameter) from the nose and throat of an infected person who is coughing and sneezing **Particles do not remain suspended in the air, and close contact (up to 3 feet) is required for transmission.**
- Direct skin-to-skin contact
- Indirect contact with respiratory secretions (touching contaminated surfaces then touching the eyes, nose or mouth).

It is presently unknown which specific mutations are needed to make the H5N1 virus easily and sustainably transmissible among humans, but potential routes whereby H5N1 might mutate and acquire human specificity do exist.

Spread within a country

Disease spreads very quickly among the population especially in crowded places. Cold and dry weather enables the virus to survive longer outside the body than in other conditions and, as a consequence, seasonal epidemics in temperate areas appear in winter.

CLINICAL SYMPTOMS

Influenza symptoms include high fever, cough, sore throat, runny nose, headache, myalgia, and often malaise. Most patients recover fully within 1-2 weeks. In comparison to other respiratory infections, such as the common cold, influenza causes more severe complications, including bacterial pneumonia, especially in children, the elderly and other high-risk groups (table 3).
Characteristic features are:

- Abrupt onset
- **Systemic symptoms:** fever, headache, myalgias (extremities, long muscles of the back; eye muscles; in children: calf muscles), malaise, prostration
- **Respiratory symptoms:** dry cough, nasal discharge - may be absent in elderly people who may present with lassitude and confusion instead
- Hoarseness, dry or sore throat often appear as systemic symptoms diminish
- Croup (only in children)

Table 3: Differences in symptomatology of influenza and cold

Symptom	Influenza	Cold
Fever	Usually high, lasts 3-4 days	Unusual
Headache	Yes	Unusual
Fatigue and/or weakness	Can last up to 2-3 weeks	Mild
Pains, aches	Usual and often severe	Slight
Exhaustion	Early and sometimes severe	Never
Stuffy nose	Sometimes	Common
Sore throat	Sometimes	Common
Cough	Yes	Unusual
Chest discomfort	Common and sometimes severe	Mild to moderate
Complications	Bronchitis, pneumonia; in severe cases life-threatening	Sinus congestion

LABORATORY DIAGNOSIS

Respiratory illness caused by influenza is difficult to distinguish from illness caused by other respiratory pathogens on the basis of symptoms alone. However, during laboratory-confirmed influenza outbreaks, the majority of persons seeking medical advice for upper respiratory tract infections are likely to be infected by influenza. Rapid diagnostic tests have recently become available that can be used to detect influenza viruses within 30 minutes.

Number of tests can help in confirming the diagnosis of influenza. During an outbreak of respiratory illness, however, testing can be very helpful in determining if influenza is the cause of the outbreak. Laboratory tests that can be carried out are:

Test method	Influenza virus types detected	Time for results
Virus culture	A and B	5-10 days
Fluorescent immunoassay	A and B	2-4 hours
RT-PCR	A and B	1-2 days
Serological test	A and B	> 2 weeks
Enzyme immunoassay (EIA)	A and B	2 hours
Rapid Antigen Detection	A; A & B	< 30 minutes

- **Detection of antigen in nasal secretions by:**
  - Rapid Test
  - Immunofluorescence test
  - Antigen capture ELISA with monoclonal antibody to the nucleoprotein
  - Reverse Transcriptase Polymerase Chain Reaction (RT-PCR)
- **Virus isolation in:**
  - Cell line Madin-Darby Canine Kidney cells (MDCK)
  - Egg inoculation
- **Serological test in paired serum samples**

In India, the facilities for laboratory diagnosis for influenza in humans are available at National Institute of Virology (NIV), Pune and NICD, Delhi. For diagnosis in animals, the facilities are available at High Security Animal Disease Laboratory (HSADL) at Bhopal and other Regional Laboratories of Department of Animal Husbandry and Dairying.

For the purpose of global surveillance, all laboratory confirmed cases of influenza A/H5 should be reported to WHO.

General bio safety measures for collection of specimens from suspected cases of human avian influenza

- Clinical samples should be collected by trained hospital / laboratory staff
- All clinical samples should be collected under special care.
- Use N95 masks while taking samples. If not available, triple layer well fitted surgical facemasks can be used.
- Use latex disposable gloves.
- Wear laboratory coat/disposable apron.
- Cover hairs with head cover.
- Use protective eyewear (goggles)/face shields if procedure is likely to generate aerosols, or splashes of secretions.
- Handle waste while collecting specimen with special precautions. The waste should be placed in an appropriate leak proof and autoclavable biohazard bag and autoclaved before disposal. Contaminated non-disposable waste should be treated properly.
- The clinical samples should be processed only in designated laboratory having the appropriate containment facilities.

Guidelines for Waste Disposal

- All the waste has to be treated as infectious waste
- Articles like swabs/gauges etc. are to be discarded in the yellow coloured autoclavable bio-safety bags. The bags are to be autoclaved followed by incineration of the contents of the bag.
- Waste like gloves, facemasks and disposable syringes etc. after use are to be discarded in blue/white autoclavable bio-safety bags, which should be autoclaved/microwaved before disposal.
- All hospitals and laboratory personnel should follow the standard guidelines *(Biomedical waste management and handling rules, 1998)* for waste management.

TREATMENT

The mainstays of treatment will include:

- General support including oxygenation, intensive care where required, antipyretics (preferably not aspirin), intravenous or oral fluids, nutrition, bed rest. These will vary depending on whether the patients are adult or paediatric, and the severity of the illness. The level of general support will vary depending on the type of facility to which the case has been admitted e.g. regional or local hospitals, special 'influenza' hospitals, nursing homes

Table 4: Recommended drugs and dosage for prophylaxis of influenza					
Antiviral	**1-6 Yrs**	**7-9 Yrs**	**10-12 Yrs**	**13-64 Yrs**	**⩾ 65 Yrs**
Amantadine	5 mg/kg/day in two divided doses	5 mg/kg/day in two divided doses	100 mg twice daily	100 mg twice daily	100 mg twice daily
Rimantadine	5 mg/kg/day in two divided doses	5 mg/kg/day in two divided doses	100 mg twice daily	100 mg twice daily	100 mg twice daily
Oseltamivir	NR*	NR*	NR*	75 mg/day	75 mg/day
*Recently oseltamivir has been cleared for prophylaxis for children > 1 yr according to their body weight; dosages same as for treatment. NR = Not recommended.					

Table 5: Recommended Daily Dosage of Antiviral Medications for Treatment of Influenza (five days)					
Antiviral agent effective against	Age groups (yrs)				
	1-6	7-9	10-12	13-64	⩾ 65
Amantadine influenza A	5 mg/kg/day up to 150 mg in 2 divided doses	5 mg/kg/day up to 150 mg in 2 divided doses	100 mg twice daily	100 mg twice daily	100 mg/day
Rimantadine influenza A	NR	NR	NR	100 mg twice daily	100 mg/day
Oseltamivir influenza A and B	Dose varies by child's weight♣	Dose varies by child's weight♣	Dose varies by child's weight♣	75 mg twice daily	75 mg twice daily
Zanamivir influenza A and B	NR	10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily
♣ for < 15 kg 30 mg twice a day; for ⩾15 to 23 kg 45 mg twice a day; for > 23 to 40 kg 60 mg twice a day; and for children > 40 kg, 75 mg twice a day. NR = Not recommended.					

- Antibiotics for bacterial complications of influenza
- Antiviral therapy (table 4 & 5), if case presents within 48 hours of disease onset (and depending on their availability within the context of pandemic requirements)
- Management of contacts may include antiviral prophylaxis and advice about relevant vaccination (e.g. pandemic strain vaccine if available).

'Technical Committee on Drugs' has recommended that following drugs can be used for treatment and chemoprophylaxis of avian flu:

- Tamiflu (Oseltamivir)
- Relenza (Zanamivir)

Never give aspirin to children and teenagers to prevent occurrence of Reye syndrome.

PREVENTION & CONTROL STRATEGIES

Respiratory etiquette:

People with respiratory infection symptoms should practice the following respiratory etiquette

All symptomatic people should:

- avoid close contact (less than 1 metre) with other people.
- cover their nose and mouth when coughing or sneezing.
- use disposable tissues to contain respiratory secretions.
- immediately dispose off used tissues in the nearest waste receptacle.

Social distancing

- Crowded places and large gatherings of people should be avoided at the time of an influenza pandemic, whether such gatherings are in open or closed spaces.
- A distance of at least 1 metre should be maintained between persons wherever possible. Greater distances are more effective.
- Any form of contact with people who are unwell with pandemic influenza, including visitors, should be avoided wherever practicable.

Protection measure	Where applicable
Hand hygiene, cough etiquette, ventilation	Everyone, all the time
Social distancing	Everyone, whenever practical
Protective barriers	In situations where regular work practice requires unavoidable and relatively close contact with the public
Disposable surgical mask	Workers in any community or health care setting who are caring for the sick (this includes first responders). Also as a possible adjunct to protective barriers
Disposable particulate respirator mask, eye protection, gloves, gown/ apron	Health care workers participating directly in patient care when there is a high risk of contact with respiratory secretions, particularly via aerosols (mostly inpatient settings).

- the emergence of such viruses will be geographically circumscribed
- the first clusters of human cases caused by the pandemic virus will be rapidly detected and reported, and the viruses will be rapidly identified and characterized
- movement of people in and out of the area will be effectively restricted to prevent further spread to unaffected areas

Antiviral drugs

WHO recommends that countries with sufficient resources should invest in a stockpile of antiviral drugs for domestic use, particularly at the start of a pandemic when mass vaccination is not possible and high-risk groups need to be protected.

The primary treatment option is the flu drug Oseltamivir (Tamiflu), a neuraminidase inhibitor that works by preventing the virus from escaping its host cell. It must be taken within two days after the appearance of symptoms.

The adamantane derivatives, amantadine and rimantadine, are chemically related, orally administered drugs that are approved for treatment and chemoprophylaxis of influenza A.

DO'S AND DON'TS FOR COMMUNITY

These guidelines are for contacts of patient's family members

Do's

- Minimize close contact with infectious case
- Use separate living, dining, bathing, laundry and toilet facilities for the infectious case, as far as possible.
- Minimize use or handling of items in home that might be used/touched by infectious case.
- Wear masks, if available or cover the nose and mouth with tissue paper or handkerchief while in close contact with infectious case (less than 3 feet) or while in a confined space.
- Always wash hands after having contact with respiratory secretions, use detergent or soap.
- Ask patient to use tissue paper/handkerchief to cover nose and mouth while coughing or sneezing.
- Ask patient to throw the tissue paper etc. always in a bin closed with a lid after its use.
- Cooperate with authorities in the event of any case, quarantine helps the health authorities to investigate the case and prevent further spread of the disease in the community.

Don'ts

- Don't handle secretions or paper, clothes used by a patient with respiratory illness.
- Don't ask people to avoid social contact with individual at risk.
- Don't indiscriminately throw the tissue paper/mask/handkerchief after use.

Quarantine

Quarantine refers to separation and restriction of activities including movement of well person(s) or animal(s) who, while not yet ill, might have been exposed or are considered to be at high risk of exposure to a case of communicable disease during its period of communicability to prevent disease transmission during the incubation period if infection should occur. The rationale behind it:

- the first viruses that show an ability to sustain transmission among humans will not yet be highly transmissible

Amantadine and rimantadine specifically inhibit replication of influenza A viruses, but not influenza B viruses. These drugs are thought to interfere with influenza A virus M2 protein, a membrane ion channel protein, and inhibit virus uncoating, which inhibits virus replication, resulting in decreased viral shedding. When administered within 48 hours of onset of illness, controlled studies have found that both drugs decrease viral shedding and reduce influenza A illness by approximately 1 day compared with placebo. The usual recommended duration of treatment is 5 days.

Strategies for the use of antivirals during a pandemic besides therapeutic use are:

- long-term pre-exposure prophylaxis for health workers etc.; and
- short-term post-exposure prophylaxis for close contacts of influenza patients

FREQUENTLY ASKED QUESTIONS (FAQ)

How is pandemic influenza spread?

Pandemic influenza spreads from person to person mainly through "respiratory secretions" like seasonal influenza viruses and other common respiratory infections. Respiratory secretions are virus-containing droplets (such as nasal secretions or sputum) that are spread when infected persons cough or sneeze. These droplets can then land on the surfaces of the mouth, nose, and throat of persons who are near (i.e., within 3 feet) to the ill person. The virus may also be spread through contact with the infectious respiratory secretions on the hands of an infected person and other objects and surfaces.

Adults can spread influenza virus one day before symptoms appear and up to five to seven days after the onset of illness while children can spread virus infection up to 10 days

Will the regular (seasonal) flu shot provide any protection against the pandemic influenza virus?

NO. The regular flu shot will protect you against the influenza viruses that are circulating right now. However in India, there is no policy for vaccination against seasonal influenza.

What can I do during a pandemic?

Community care

- In case of pandemic, there may be scarcity of hospital beds but most exposed cases could be taken care of, at home
- People with respiratory infection symptoms should practise the following whenever they are in the presence of another person. All symptomatic people should follow:
  - respiratory ettiquettes
  - social distancing

Home Care

- Take extra rest. Bed rest can help you feel better. It will also help you avoid spreading the virus to others.
- Drink plenty of fluids to replace those lost due to fever. Fluids also ease a scratchy throat and keep nasal mucus thin. Hot tea with lemon, water, fruit juice, and soup are all good choices.
- If fever is uncomfortable, take paracetamol to lower it. You may also sponge your body with lukewarm water to reduce fever. Do not use cold water or ice. Lowering the fever will not make your symptoms go away faster, but it may make you more comfortable.
- To relieve body aches and headache, take paracetamol. Do not take aspirin if you are younger than 20, unless your doctor tells you to do so. Also, aspirin can upset your stomach.
- Try a decongestant or nasal spray if your main symptom is a stuffy nose. Look for a single-ingredient decongestant that contains phenylephrine. If nasal drainage is thick, a decongestant that contains guaifenesin may help keep it thin and draining. Do not use medicated nasal sprays or drops more often than directed and not for longer than 3 days.
- Breathe moist air from a steam inhaler or a pan filled with hot water to help clear a stuffy nose.
- Avoid antihistamines. They do not treat flu symptoms and may make nasal drainage thicker.
- If the skin around your nose and lips becomes sore from repeated rubbing with tissues, apply a bit of petroleum jelly to the area. Using disposable tissues that contain lotion may also help.
- Use cough syrup or plain, hard candy to help ease coughing.
- Take a nonprescription cough medicine that contains dextromethorphan if you develop a dry, hacking cough. Some products contain a high percentage of alcohol. Use them with caution.
- Elevate your head at night with an extra pillow if coughing keeps you awake.
- Avoid smoking and breathing second hand smoke. This is good advice any time, but it is especially important when you have a respiratory infection like a cold or the flu.

Call your doctor if:

- Your symptoms improve but then seem to get worse again.
- You develop signs of a bacterial infection, such as a new or worse cough that produces yellow, green, rust-colored, or bloody mucus; persistent fever, ear pain, sore throat, sinus pain, or productive cough; or nasal drainage that changes from clear to colored after 7 to 10 days.

THINGS YOU NEED TO KNOW ABOUT PANDEMIC INFLUENZA

1. Pandemic influenza is different from avian influenza

Avian influenza refers to a large group of different influenza viruses that primarily affect birds. On

rare occasions, these bird viruses can infect other species, including pigs and humans. The vast majority of avian influenza viruses do not infect humans. Influenza pandemic happens when a new subtype emerges that has not previously circulated in humans.

2. Influenza pandemics are recurring events

Influenza pandemic is a rare but recurrent event. Three pandemics occurred in the previous century: "Spanish influenza" in 1918, "Asian influenza" in 1957, and "Hong Kong influenza" in 1968. The 1918 pandemic killed an estimated 50-100 million people worldwide. That pandemic, which was exceptional, is considered one of the deadliest disease events in human history.

Subsequent pandemics were much milder, with an estimated 2 million deaths in 1957 and 1 million deaths in 1968.

Because the virus is new, the human immune system will have no pre-existing immunity. This makes it likely that people who contract pandemic influenza will experience more serious disease than that caused by normal influenza.

3. The world may be on the brink of another pandemic

Health experts have been monitoring a new and extremely severe influenza virus - the H5N1 strain - for almost eight years. This strain first infected humans in Hong Kong in 1997, causing 18 cases, including six deaths. Since then, over 258 human cases have been laboratory confirmed and more than half (153) of these people have died. Most cases have occurred in previously healthy children and young adults. Fortunately, the virus does not jump easily from birds to humans or spread readily and sustainably among humans. If H5N1 evolves to a form as contagious as normal influenza, a pandemic could begin.

4. All countries will be affected

Once a fully contagious virus emerges, its global spread is considered inevitable. Countries might delay arrival of the virus, but cannot stop it. The pandemics of the previous century encircled the globe in 6 to 9 months, even when most international travel was by ship. Given the speed and volume of international air travel today, the virus could spread more rapidly, possibly reaching all continents in less than 3 months.

5. Widespread illness will occur

Because most people will have no immunity to the pandemic virus, infection and illness rates are expected to be higher than during seasonal epidemics of normal influenza. Current projections for the next pandemic estimate that a substantial percentage of the world's population will require some form of medical care. Few countries have the staff, facilities, equipment, and hospital beds needed to cope with large numbers of people who suddenly fall ill.

6. Medical supplies will be inadequate

Supplies of vaccines and antiviral drugs - the two most important medical interventions for reducing illness and deaths during a pandemic - will be inadequate in all countries at the start of a pandemic and for many months thereafter. Inadequate supplies of vaccines are of particular concern, as vaccines are considered the first line of defence for protecting populations.

7. Large numbers of deaths will occur

Historically, the number of deaths during a pandemic has varied greatly. Death rates are largely determined by four factors: the number of people who become infected, the virulence of the virus, the underlying characteristics and vulnerability of affected populations, and the effectiveness of treatment and other preventive measures. Accurate predictions of mortality cannot be made before the pandemic virus emerges and begins to spread. All estimates of the number of deaths are purely speculative.

8. Economic and social disruption will be great

High rates of illness and worker absenteeism are expected, and these will contribute to social and economic disruption. Not all parts of the world or of a single country are expected to be severely affected at the same time. Social disruption may be greatest when rates of absenteeism impair essential services, such as power, transportation, and communications.

...about CD*Alert*

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Chief Editor: Dr. R. K. Srivastava

Editorial Board: Dr. Shiv Lal, Dr. R. L. Ichhpujani, Dr. Shashi Khare, Dr. A. K. Harit

Guest Editor: Dr. Avdhesh Kumar, Dr. A.C. Dhariwal, Dr. Sharayu Gaekwad

Publisher: Director, National Institute of Communicable Diseases, 22 Shamnath Marg, Delhi 110 054
Tel: 011-23971272, 23971060 Fax : 011-23922677
E-mail: dirnicd@bol.net.in and dirnicd@del3.vsnl.net.in

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