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Influenza Pandemic Plan. The Role of WHO and Guidelines for National and Regional Planning

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1 Executive summary

This document has been prepared to assist medical and public health leaders to better respond to future threats of pandemic influenza. It outlines the separate but complementary roles and responsibilities for the World Health Organization (WHO) and for national authorities when an influenza pandemic appears possible or actually occurs. Specific descriptions are given of the actions to be taken by WHO as it assesses the risk posed by reported new sub-types of influenza, in advance of any epidemic spread. The responsibility for management of the risk from pandemic influenza, should it actually occur, rests primarily with national authorities. WHO strongly recommends that all countries establish multidisciplinary National Pandemic Planning Committees (NPPCs), responsible for developing strategies appropriate for their countries in advance of the next pandemic.

In recognition of the individuality of countries, as well as the unpredictability of influenza, this document emphasizes the processes and issues appropriate for WHO and NPPCs, but does not provide a "model plan". Furthermore, it is anticipated that NPPCs will confront new issues, which will call for additional international dialogue. For example, more consideration is needed about how scarce supplies of vaccines can be shared, and what might be the benefit of cancelling public gatherings to slow the spread of a pandemic virus among unvaccinated populations.

It is impossible to anticipate when a pandemic might occur. Should a true influenza pandemic virus again appear that behaved as in 1918, even taking into account the advances in medicine since then, unparalleled tolls of illness and death would be expected. Air travel could hasten the spread of a new virus, and decrease the time available for preparing interventions. Health care systems could be rapidly overburdened, economies strained, and social order disrupted. Although it is not considered feasible to halt the spread of a pandemic virus, it should be possible to minimize the consequences by having prepared for the challenge in advance.

Even in the absence of a pandemic, as was seen in the US in 1976 and in Hong Kong SAR in late 1997, there can be rapid build up of public fear about even the *possibility* of a pandemic when a few cases of infection in humans with a new virus sub-type occur. Such fears about the existence of a dangerous new form of influenza virus create major challenges for health authorities and national leaders, even while epidemic spread of a new virus remains unconfirmed. To better cope with "false alarms" resulting from intensive surveillance, a series of "Preparedness Levels" have been defined that can be applied before the beginning of a pandemic is declared. This should assist WHO to report on novel virus infections of humans and initiate precautionary responses, without creating unnecessary panic. Such a need is particularly important in an age when information is so rapidly shared by electronic means. Special efforts should continue to be made to expand the capabilities for use of electronic communications by those conducting surveillance or assessing and managing the response to new influenza viruses, and for the orderly dissemination of situation reports.

This document is available on the World Health Organization website,
at http://www.who.int/emc/diseases/flu/index.html

2 Introduction

During inter-pandemic periods, influenza viruses circulate that are related to those from the preceding epidemic. The viruses are spreading among people with varying levels of immunity from infections earlier in life. Such circulation, over a period of usually 2-3 years, promotes the selection of new strains which have changed enough to again cause an epidemic among the general population; this process is termed "antigenic drift". "Drift variants" may have different impacts in different communities, regions, countries or continents in any one year, although over several years their overall impact is often similar. Typical influenza epidemics cause increases in incidence of pneumonia and lower respiratory disease as witnessed by excess rates of hospitalization or mortality. The elderly or those with underlying chronic diseases are most likely to experience such complications, but young infants also may suffer severe disease. The morbidity caused by influenza viruses is described in Annex A.

At unpredictable intervals, however, novel influenza viruses emerge with a key surface antigen (the haemagglutinin) of a totally different sub-type from strains circulating the year before. This phenomenon is called "antigenic shift". If such viruses have the potential to spread readily from person-to-person, then more widespread and severe epidemics may occur, usually to a similar extent in every country within a few months to a year, resulting in a pandemic. Annex B provides more information on these issues, and Annex C discusses hypotheses about the origin of pandemic viruses.

In summary, each past pandemic resulted from:

- the emergence of an influenza A virus with a different haemagglutinin sub-type than strains circulating in humans for many preceding years, and
- a high proportion of susceptible people in the community, i.e., no or low antibody titres to the haemagglutinin of the novel virus detected in major segments of the population, and
- high person-to-person transmissibility of the new virus, with accompanying human disease

The pandemics this century were in 1918, 1957, 1968 and to a lesser extent, in 1977 (Table 3, Annex B). The pandemic of 1918/19 was the most severe; an estimated 20 million people died worldwide.

In addition, there have been "false alarms" (Table 3, Annex B). For example, in the US in 1976 a localized outbreak, with a fatal index case, occurred among military recruits. This death was due to an influenza virus similar to that found in US swine. Such viruses are related to those that caused the 1918 pandemic. Response in the US included large-scale vaccine production under government contract, and a mass vaccination campaign. However, the virus did not spread outside the training camp. Sporadic cases of swine influenza virus infection in humans have been detected in the US on several other occasions (e.g., in Wisconsin in 1988). Other examples

described in the lower part of Table 1 probably reflect the tip of the iceberg. Early warning of unusual or unexpected cases will rely upon a well-functioning veterinary and human influenza surveillance system.

Again in 1997 there was concern about a potential pandemic when human cases of an H5N1 virus sub-type were detected in Hong Kong SAR. The H5N1 viruses found in humans related to viruses isolated from sick chickens in Hong Kong SAR. However, intensive investigations failed to confirm efficient person-to-person transmission of the virus, and the human infections stopped when public health officials and veterinarians organized mass destruction of chickens from markets and their breeding farms.

Preparation of high growth reassortants for the production of an H5N1 vaccine strain has been shown to be difficult and time consuming, due to technical problems encountered during the selection processes (e.g., toxicity to the embryonated hen's eggs). More than 12 months elapsed after the occurrence of the index case in May 1997 before such reagents were available for experimental vaccine production. This is to remind us that the rapid production of a suitable vaccine effective against a pandemic influenza strain might not be at hand and alternative control measures have to be thought of in advance.

These different histories show the need for flexible contingency plans capable of responding efficiently to a pandemic threat. The purpose of this document is to provide information and a framework to assist WHO and its Member States to be prepared to fulfil their roles and responsibilities in this regard.

3 The role of the World Health Organization (WHO)

In addition to its role in collecting and analysing data on the occurrence of influenza viruses around the world, WHO continuously provides information to health authorities, the media and the general public about current influenza vaccine recommendations, as well as of currently available anti-virals, through one of more of the following methods:

http://www.who.int/emc/diseases/flu/index.html

- maintaining up-to-date summary reports on the WHO World Wide Web site (FluNet),

http://www.who.int/wer/index.html

- reporting in the Weekly Epidemiological Record,
- informing national health authorities, national influenza centres and other participants in the influenza program about the global influenza situation,
- developing proposals to help guide national policy makers or those implementing national policies, and

http://www.who.int/inf

- issuing press releases.

3.1 Assessing the level of alert from novel influenza viruses during inter-pandemic periods

A new pandemic virus may first be detected from significant and rapidly spreading outbreaks, as for example in 1957 and 1968. Nevertheless, it is important for effective planning to have a process which defines responses to alternative possibilities, such as the recognition of a new virus which does *not* spread and cause a pandemic, and the early detection of low-level spread of a true pandemic virus.

The definition of Preparedness Levels described here provides a basis for WHO to determine its response to such situations as they are assessed.

Preparedness Levels 1, 2 and 3 correspond to events that would be occurring in an inter-pandemic period (which also may be stated to correspond to Pandemic Phase 0). Accordingly, WHO will maintain a Pandemic Task Force during inter-pandemic periods to initiate appropriate measures, where a possible pandemic virus is reported, and to describe the level of preparedness believed to exist (*see below and the accompanying Table 1*).

The recognition of a new virus which *does* spread in humans will lead to the declaration by WHO, with the help of its task force and after international consultation, of a new influenza pandemic.

3.2 Phase 0: Inter-pandemic activities

During this phase, no indications of any new virus type have been reported. As mentioned above, the inter-pandemic period, when new haemagglutinin sub-types of influenza A viruses with pandemic potential may emerge, is considered to be Pandemic Phase 0. Based on reports about such new viruses submitted to the WHO, and review by its Pandemic Task Force and other experts, WHO will report on the subsequent phases of the pandemic as each occurs.

See Annex F for address information

http://www.who.int/emc/diseases/flu/centres.html

During the inter-pandemic period, WHO co-ordinates a program of international surveillance for influenza in humans, with the assistance of four WHO Collaborating Centres (CCs). The Centres are based in Atlanta, USA; London, UK; Melbourne, Australia; and Tokyo, Japan. These Centres maintain repositories of different virus strains, develop reagents and technologies for strain comparisons, and train workers from national laboratories. Furthermore, the Centres have bio-containment facilities which enable them to conduct studies with possible pandemic viruses under conditions that do not pose safety risks or jeopardize the analysis.

See Annex F for address information

http://www.who.int/emc/diseases/flu/centres.html

The National Influenza Laboratories designated by WHO are the "front lines" of surveillance activities. These exist in many countries and are equipped to perform virus isolation in eggs or tissue culture, and to identify virus isolates by haemagglutination inhibition tests. Many also can perform rapid laboratory diagnosis by antigen detection methods (e.g., fluorescence microscopy on pharyngeal swabs), and titration of antibodies in human sera. WHO currently provides each of these national laboratories with a kit of reagents, prepared by the WHO CC in Atlanta, for typing influenza isolates. Results are reported to WHO, and samples of the isolates are meanwhile sent to the Collaborating Centres for careful comparisons with each other, and with older strains. In this way the appearance and spread of new variants can be confirmed definitively, and the relative importance of new variants judged.

When indicated, candidates for vaccine production are selected by the Collaborating Centres and National Control Authorities from Australia and Oceania, Europe, Asia, and the US in time for vaccine formulation recommendations. These recommendations are drawn up at two annual meetings of experts who review data for the recommendations of vaccines: in February for the Northern and in September for the Southern Hemisphere. More information about the process of recommending and manufacturing influenza vaccines is provided in Annex D.

WHO has also designated a Collaborating Centre for the study of animal influenza viruses; this Centre is based in Memphis, Tennessee, USA, and assists WHO in identifying viruses isolated from different animal species, and by research into the relationship between human and animal strains.

3.2.1 Phase 0, Preparedness Level 1, new influenza strain in a human case

This Preparedness Level will exist following the first report(s) of isolation of a novel virus sub-type from a single human case, without clear evidence of spread of such a virus or of outbreak activity associated with the new virus.

- WHO will announce with the help of its task force and after international consultation this Preparedness Level 1.

- WHO will co-ordinate international efforts to assist national and local authorities reporting the potential pandemic virus in confirming the infection of a human by a novel strain by:

  Excluding laboratory errors or artefacts as a cause of the report, such as unsuspected laboratory contamination of a specimen or incorrect laboratory procedures;

  Seeking additional data concerning sources of exposure, infection of contacts, and existence of antibody responses in persons exposed to the novel virus, including members of the household, school or workplace of the index case(s), health care workers, and laboratory workers;

  Attempting re-isolation of the virus from original clinical specimens, into a substrate acceptable for developing a vaccine seed virus;

  Applying techniques of molecular biology to sequence virus genes and to prepare viral genome copies from original clinical specimens, to use for genetic modifications if necessary;

  Evaluating the sensitivity of the new isolate(s) to available anti-viral drugs.

- WHO will heighten activities of the laboratory surveillance network by:

  Advising national influenza laboratories to immediately review their results and report the presence of viruses that appear difficult to type;

  Expediting shipment of samples of such possible new virus isolates to and among Collaborating Centres, including facilitating customs clearance if necessary;

  Promoting development and planning for distribution of reagents to all national influenza laboratories for identification of the novel virus strain.

3.2.2 Phase 0, Preparedness Level 2, human infection confirmed

This Preparedness Level will exist when it has been confirmed that two or more human infections have occurred with a new virus sub-type, but the ability of the virus to readily spread from person-to-person and cause multiple outbreaks of disease leading to epidemics remains questionable.

- WHO will announce with the help of its task force and after international consultation this Preparedness Level 2.

- WHO will encourage and assist the country, where initial cases were detected, to enhance surveillance and diagnosis, and organize special investigations designed to increase understanding of the possible transmission and impact of the new virus.

- WHO will develop a case definition to be used in surveillance for a new virus sub-type, particularly during early stages of virus spread.

- WHO will invite if necessary a group of countries to participate in determination of the prevalence of antibody to the new virus in the general population. To ensure comparability of findings, a reference laboratory for serological tests will be designated.

- WHO will promote enhanced surveillance activity regionally or internationally. National laboratories, especially those in countries where the population has considerable travel-related contact with the site of initial identification of the novel virus, will be encouraged to increase reporting of possible clusters or outbreaks of influenza-like illness, and to arrange timely laboratory diagnosis, regardless of whether it is the normal "influenza season".

- WHO will recommend that national health authorities take contingency steps that will facilitate activation of their national pandemic preparedness plans, if this becomes necessary.

- WHO will promote development and evaluation of candidates for production of vaccines against the novel influenza strain, using approaches such as the following, as appropriate:

  If feasible, high growth and cold-adapted attenuated reassortant viruses will be prepared, with precautions to ensure their handling does not pose threats to humans or susceptible animals when grown in current types of vaccine production facilities that use chicken eggs;

Pre-existing laboratory-adapted strains antigenically and biologically suitable for vaccine production against the novel virus may be identified (e.g., similar isolates from animal hosts);

Laboratory-adapted variants may be prepared with the new virus, such as by multiple passage in different hosts or at different temperatures, to select variants that could be safely and successfully used for vaccine production.

In the future, awaiting technological improvements, genetic engineering may be undertaken to delete or modify parts of the viral nucleic acid that are required for virulence, such as a haemagglutinin cleavage site, thereby producing a seed virus for vaccine production in normal host systems. Through genetic engineering new forms of vaccine production technology may be possible, dependent on expression of cloned nucleic acid. Accordingly,

- WHO will promote development of reagents necessary to determine the identity and potency of vaccines prepared with the new strain.

- WHO will promote contingency planning for pre-clinical and clinical trials of vaccines, such as seeking locations with the ability to undertake such trials with different types of vaccines that might become available, and identifying persons to serve on a technical advisory group for the design, conduct and interpretation of such trials.

3.2.3 Phase 0, Preparedness Level 3, human transmission confirmed

This Preparedness Level will exist when human transmission of the new virus sub-type has been confirmed through clear evidence of person-to-person spread in the general population, such as secondary cases resulting from contact with an index case, with at least one outbreak lasting over a minimum two week period in one country. Identification of the new virus sub-type in several countries, with no explanation other than contact among infected people, may also be used as evidence for significant human transmission.

Before WHO announces this Preparedness Level, the WHO task force will have ensured that an international consultation has occurred: first, to ensure that the assessment of the new virus' pandemic potential is not overlooking any other explanation, including artificial exposure of humans in several locations to an influenza virus (e.g., an act of terrorism), or an unusual ecological situation with an animal vector spreading virus to humans in different locations; and second, to be assured that the potential of the virus to cause lower respiratory tract disease or other complications is evident.

- WHO with the help of its task force and after international consultation announces this Preparedness Level 3.

- WHO will disseminate the case definition to be used in surveillance for the new virus sub-type.

- WHO will facilitate the distribution to all interested manufacturers of candidate vaccine viruses developed as part of the Preparedness Level 2 activities.

- WHO will convene its experts for influenza vaccine composition to develop, disseminate and encourage co-ordinated clinical trials of vaccines against the new strain.

- WHO will convene its experts for vaccine composition to develop ways most likely to make vaccines widely available throughout the world, with recommendations for their use appropriate to the populations, health care delivery systems and environments in different regions.

- WHO will further enhance its information dissemination to provide timely reports of the status of investigations of the new virus, its spread, and the development of responses to it.

- WHO will contact vaccine manufacturers and national governments about capacity and plans for production and international distribution of a vaccine to the new virus.

- WHO will encourage international co-ordination for purchase and distribution of vaccine among different countries.

- WHO will provide general guidelines to national health authorities based on the best available information to assist individual countries that are determining their course of action. Guidance is expected to be helpful, particularly with regard to the following aspects:

  Types of surveillance most likely to reliably document spread and impact of the new virus;

  Risk groups for contracting infection or suffering severe morbidity;

  Situation with regard to plans for manufacturing vaccine against the new virus;

  Other approaches to control; and,

  Case management.

3.3 Phase 1: Confirmation of onset of pandemic

The Pandemic will be declared when the new virus sub-type has been shown to cause several outbreaks in at least one country, and to have spread to other countries, with consistent disease patterns indicating that serious morbidity and mortality is likely in at least one segment of the population. Onset shall be defined as that point in time when WHO has confirmed that a virus with a new haemagglutinin sub-type compared to recent epidemic strains is beginning to spread from one or more initial foci. Depending on the amount of early warning, this phase may or may not have been preceded by the above-described series of increasing levels of preparedness.

- WHO with the help of its task force and after international consultation announces the onset of a new influenza pandemic: Phase 1.

- WHO will make recommendations for composition and use of vaccines (doses and schedules), and organize consultations that are intended to facilitate vaccine production and distribution in the most equitable manner possible. WHO would also consider the situation where a new virus sub-type had not replaced previously circulating strains.

- WHO will issue guidance on the best use of available anti-viral drugs against the new virus.

- National response measures should be initiated as rapidly as possible according to pre-determined national pandemic plans, updated to take account of specific characteristics of the new sub-type and knowledge of vaccine availability.

- WHO will further enhance its monitoring and reporting of the global spread and impact of the virus.

- WHO will seek support in mobilization of resources for countries with limited capacities through partnership with organizations such as UNICEF, the International Federation of Red Cross and Red Crescent Societies, the World Bank, and international relief agencies.

- WHO will work with regional offices as appropriate to encourage common activities among nations facing similar challenges from the pandemic.

3.4 Phase 2: Regional and multi-regional epidemics

Outbreaks and epidemics are occurring in multiple countries, and spreading region by region across the world.

- WHO with the help of its task force and after international consultation announces the onset of the influenza pandemic Phase 2.
- WHO will continue to work with regional offices as appropriate to encourage common activities among nations.
- WHO will continue monitoring and reporting of the global spread and impact of the virus.
- WHO will continue to organize the distribution of vaccines in the most equitable manner possible.
- WHO will update guidance on the best use of available anti-viral drugs against the new virus.
- WHO will seek further support in mobilization of resources for countries with limited capacities.

3.5 Phase 3: End of the first pandemic wave

The increase in outbreak activity in the initially affected countries or regions has stopped or reversed, but outbreaks and epidemics of the new virus are still occurring elsewhere.

- WHO with the help of its task force and after international consultation announces the onset of the influenza pandemic Phase 3.
- WHO will continue to work with regional offices as appropriate to encourage common activities among nations.
- WHO will continue monitoring and reporting of the global spread and impact of the virus.

- WHO will continue to organize the distribution of vaccines in the most equitable manner possible.

- WHO will update guidance on the best use of available anti-viral drugs against the new virus.

- WHO will seek further support in mobilization of resources for countries with limited capacities.

3.6 Phase 4: Second or later waves of the pandemic

Based on past experiences, at least a second severe wave of outbreaks caused by the new virus would be expected to occur within 3-9 months of the initial epidemic in many countries.

- WHO with the help of its task force and after international consultation announces the onset of the influenza pandemic Phase 4.

- WHO will continue monitoring and reporting of the global spread and impact of the virus.

- WHO will estimate the remaining needs for vaccines.

- WHO will estimate the availability of anti-viral drugs.

- WHO will seek further support in mobilization of resources for countries with limited capacities.

3.7 Phase 5: End of the pandemic (back to Phase 0)

WHO will report when the Pandemic Period has ended, which is likely to be after 2-3 years. The indications for this will be that that indices of influenza activity have returned to essentially normal inter-pandemic levels, and that immunity to the new virus sub-type is widespread in the general population. Major epidemics would not be expected again until antigenic variants begin to emerge from the prototype pandemic strain.

- WHO with the help of its task force and after international consultation will declare the end of the influenza pandemic, and the onset of a new inter-pandemic phase: Phase 0.

The methods used by WHO for collecting information about the occurrence of influenza, reporting on the spread of the virus, and promoting implementation of special control measures will generally return to pre-pandemic levels. Where it appears advantageous, on the basis of experience obtained during the pandemic period, and consistent with resources available, WHO and/or individual country activities, related to influenza control may remain augmented.

3.8 WHO actions in the post-pandemic phase

After the pandemic period has been declared by WHO to be over, WHO will organize consultations and meetings to undertake the following:

- Assessment of the overall impact of the pandemic.
- Evaluation of lessons learned from the pandemic that will assist in responding to future pandemics.
- Update of the WHO influenza Pandemic Plan.

TABLE 1: PREPAREDNESS LEVELS FOR INTER-PANDEMIC, PANDEMIC AND POST-PANDEMIC PERIODS

	PHASE	CHARACTERIZED BY:	EXPLANATION	ACTIONS TO BE TAKEN BY WHO
INTER-PANDEMIC PERIOD	**PHASE 0**		No indications of any new virus type have been reported	WHO will: **co-ordinate** a program of international surveillance for influenza in humans, with the assistance of four Collaborating Centres.
	PHASE O, PREPAREDNESS LEVEL 1	Appearance of a new influenza strain in a human case	This Preparedness Level will exist following the first report(s) of isolation of a novel virus sub-type, without clear evidence of spread of such a virus or of outbreak activity associated with the new virus.	**announce**, with the help of its task force and after international consultation, this Preparedness Level 1. **co-ordinate** international efforts to assist national and local authorities reporting the potential pandemic virus in confirming the infection of a human by a novel strain. **heighten** activities of the laboratory surveillance laboratory network.
	PHASE O, PREPAREDNESS LEVEL 2	Human infection confirmed	This Preparedness Level will exist when it has been confirmed that two or more human infections have occurred with a new virus sub-type, but where the ability of the virus to readily spread from person-to-person and cause multiple outbreaks of disease leading to epidemics remains questionable.	**announce**, with the help of its task force and after international consultation, this Preparedness Level 2. **encourage** and assist the country, where initial cases were detected, to enhance surveillance and diagnosis, and organize special investigations designed to increase understanding of the possible transmission and impact of the new virus. **develop** a case definition to be used in surveillance for a new virus sub-type. **invite** a group of countries to participate in determination of the prevalence of antibody to the new virus in the general population. **promote** enhanced surveillance activity regionally or internationally. **promote** development and evaluation of candidates for production of vaccines against the novel influenza strain. **promote** development of reagents necessary to determine the identity and potency of vaccines prepared with the new strain. **promote** contingency planning for pre-clinical and clinical trials of vaccines. **promote** the development of strategies for the most efficient use of newly developed vaccines. **recommend** that national health authorities take contingency steps that will facilitate activation of their National Pandemic Preparedness Plans.

TABLE 1: PREPAREDNESS LEVELS FOR INTER-PANDEMIC, PANDEMIC AND POST-PANDEMIC PERIODS, continued

PHASE	CHARACTERIZED BY:	EXPLANATION	ACTIONS TO BE TAKEN BY WHO	
PHASE O, PREPAREDNESS LEVEL 3	Human transmission confirmed	This Preparedness Level will exist when human transmission of the new virus sub-type has been confirmed through clear evidence of person-to-person spread in the general population, such as secondary cases resulting from contact with an index case, with at least one outbreak lasting over a minimum two week period in one country.	**announce**, with the help of its task force and after international consultation, Preparedness Level 3. **disseminate** the case definition to be used in surveillance for the new virus sub-type. **facilitate** the distribution to all interested manufacturers of candidate vaccine viruses developed as part of the Preparedness Level 2 activities. **convene** its experts for influenza vaccine composition to develop, disseminate and encourage co-ordinated clinical trials of vaccines against the new strain. **convene** its experts for vaccine composition to develop ways most likely to make vaccines widely available throughout the world. **enhance** further its information dissemination to provide timely reports of the status of investigations of the new virus, its spread, and the development of responses to it. **contact** vaccine manufacturers and national governments about capacity and plans for production and international distribution of a vaccine to the new virus. **encourage** international co-ordination for purchase and distribution of vaccine among different countries. **provide** general guidelines to national health authorities based on the best available information to assist individual countries that are determining their course of action.	INTER-PANDEMIC PERIOD
PHASE 1	Confirmation of onset of pandemic	The onset of a new pandemic will be declared when WHO has confirmed that a virus with a new haemagglutinin sub-type compared to recent epidemic strains is beginning to cause several outbreaks in at least one country, and to have spread to other countries, with consistent disease patterns indicating that serious morbidity and mortality is likely in at least one segment of the population.	**announce**, with the help of its task force and after international consultation, the onset of a new influenza Pandemic: Phase 1. **make** recommendations for composition and use (doses and schedules) of vaccines, and organize consultations that are intended to facilitate vaccine production and distribution in the most equitable manner possible. **issue** guidance on the best use of available anti-viral drugs against the new virus. **national** response measures should be initiated as rapidly as possible according to pre-determined national pandemic plans, updated to take account of specific characteristics of the new sub-type and knowledge of vaccine availability. **enhance** further its monitoring and reporting of the global spread and impact of the virus. **seek** support in mobilization of resources for countries with limited capacities through partnership with different organizations and international relief agencies. **work** with regional offices as appropriate to encourage common activities among nations facing similar challenges from the pandemic.	PANDEMIC PERIOD

TABLE 1: PREPAREDNESS LEVELS FOR INTER-PANDEMIC, PANDEMIC AND POST-PANDEMIC PERIODS, continued

	PHASE	CHARACTERIZED BY:	EXPLANATION	ACTIONS TO BE TAKEN BY WHO
PANDEMIC PERIOD	**PHASE 2**	Regional and multi-regional epidemics	This Preparedness Level will exist when outbreaks and epidemics are occurring in multiple countries, and spreading region by region across the world.	**announce**, with the help of its task force and after international consultation the onset of the influenza Pandemic: Phase 2. **continue** to work with regional offices as appropriate to encourage common activities among nations. **continue** monitoring and reporting of the global spread and impact of the virus. **continue** to organize the distribution of vaccines in the most equitable manner possible. **update** guidance on the best use of available anti-viral drugs against the new virus. **seek** further support in mobilization of resources for countries with limited capacities.
	PHASE 3	End of first pandemic wave	The increase in outbreak activity in the initially affected countries or regions has stopped or reversed, but outbreaks and epidemics of the new virus are still occurring elsewhere.	**announce**, with the help of its task force and after international consultation, the onset of the influenza Pandemic: Phase 3. **continue** to work with regional offices as appropriate to encourage common activities among nations. **continue** monitoring and reporting of the global spread and impact of the virus. **continue** to organize the distribution of vaccines in the most equitable manner possible. **update** guidance on the best use of available anti-viral drugs against the new virus. **seek** further support in mobilization of resources for countries with limited capacities.
	PHASE 4	Second or later waves of the pandemic	Based on past experiences, at least a second severe wave of outbreaks caused by the new virus would be expected to occur within 3-9 months of the initial epidemic in many countries.	**announce**, with the help of its task force and after international consultation, the onset of the influenza Pandemic: Phase 4. **continue** monitoring and reporting of the global spread and impact of the virus. **estimate** the remaining needs for vaccines. **estimate** the availability of anti-viral drugs. **seek** further support in mobilization of resources for countries with limited capacities.
POST-PANDEMIC PERIOD	**PHASE 5**	End of the pandemic (back to Phase 0)	WHO will report when the Pandemic Period has ended, which is likely to be after 2-3 years.	**Assessment** of the overall impact of the pandemic. **Evaluation** of "lessons learned" from the pandemic that will assist in responding to future pandemics. **Update** of the WHO influenza Pandemic Plan.

4 The role of national health authorities and pandemic planning committees

All countries should establish a **National Pandemic Planning Committee** (NPPC). This committee should be a permanent body whose responsibilities would vary according to the global and national influenza situation. During inter-pandemic periods, this committee would overview the normal response to the periodic appearance of influenza. The role of this committee becomes particularly vital when WHO confirms the presence of a new virus and its potential for human transmission. National authorities should periodically report on the progress of their NPPCs to WHO, and provide copies of their pandemic plans. WHO, if appropriate, will convene regional meetings to work with national representatives on plan development.

4.1 Composition of the national pandemic planning committee (NPPC)

The composition and functioning of an NPPC are not rigid, and may vary according to the institutional and political structures present in each country. The types of organizations or experts suggested to be represented on or consulted by the NPPC are listed below. To keep the committee to a manageable size, a core group may be selected as "permanent members", with others participating on occasions when their expertise or input is required, or consulted during the process without attending meetings:

- national and regional public health authorities, including preventive, curative and diagnostic services, the national drug regulatory authority, and the National Influenza Centre(s)
- representatives of associations of physicians (e.g., General Practitioners and Respiratory Physicians), nurses, and pharmacists
- important national virologists and epidemiologists and representatives of scientific and university institutions
- veterinary authorities and experts in animal influenza viruses
- representatives of public or private organizations that monitor health indicators, use of health care facilities and pharmaceuticals
- representatives of pharmaceutical manufacturers or distributors
- representatives of social services administrations
- representatives of military or other government emergency response organizations or teams

- representatives of non-governmental and voluntary organizations, such as the national Red Cross or Red Crescent Society

- representatives of telecommunications and media relations experts

Occupational health specialists, possibly psychologists, experts in medical ethics, and leaders of major religious groups may also be able to contribute to the planning process. Leaders among the business, educational, sporting and other recreational communities can also be considered for participation or consultation.

4.2 Establishing an effective management process

Responding to an alert such as a pandemic requires effective administration. A management process should be agreed to from the beginning by the NPPC, which would include setting up the chain of command necessary to ensure smooth functioning during the emergency. The methods for keeping the committee in contact via up-to-date telephone or e-mail lists and for identifying alternates and replacement members need to be clear. Procedures for putting the committee on alert if WHO announces a Level 2 Pandemic Preparedness should be established, as well as the way the committee would function in the event the preparedness level escalates and a pandemic begins. Time frames should be established for completing and implementing the various elements of the national pandemic plan, and for their review and update on a continuous basis.

4.3 Deciding on vaccination strategy

One of the key decisions each National Pandemic Planning Committee must take is recommending the extent of vaccination intervention possible in the event of a pandemic, bearing in mind the resources available (*see Table 2*). The Committee should address this question early in its deliberations, since its decision will condition many of the other issues to be addressed later (*see below and Section 5, as well as Annex D*).

4.4 Planning an overall control strategy

The National Pandemic Planning Committee should draft overall contingency plans for responses to a pandemic. Where regional plans already exist, they should be consulted. In regional areas where countries are contiguous, exchange of regional plans is recommended. Several contingency plans might be required to account for the season when a new sub-type is first identified, its proximity to the country, the information available about its impact, and the degree to which prevention measures will be attempted. For each of the selected responses to be included, time frames for action steps and approximate budgets should be developed. Contingency plans should deal with various attack rates: 10% would be stressful for the community, 25% would disrupt community services and stress hospital and medical care facilities, 50% would be disastrous.

For many issues, there may already be adequate information from which to begin planning from existing disaster and emergency plans: e.g., structure of the population, availability of regular and emergency medical facilities and workers,

pharmaceutical distribution system and similar relevant information, together with descriptions of procedures for initiating emergency measures.

Inevitably not all information desired would exist, and the process of developing a response to a pandemic will likely highlight areas of weakness in the national infrastructure for dealing with it. By noting these weaknesses, it may prove possible to stimulate research or enquiry, as well as actual infrastructure improvement, well in advance of a pandemic alert or possible alert. Countries may also wish to benefit from outside assistance in determining what measures to adopt and developing their plans accordingly. The convening of meetings with assistance from WHO may be essential to help place the pandemic challenge in a regional context, so that needs common to the region can be addressed with compatible and mutually reinforcing strategies.

4.5 Strengthening surveillance systems

Decisions will be critically dependent on data about the occurrence, spread and impact of a new influenza virus sub-type. The types of data needed, and the technological means to rapidly collect and access such information, need to be carefully defined. Special attention needs to be given to obtaining laboratory equipment, and preparing procedures and training programs, to permit diagnostic and vaccine development work with a new sub-type that may be highly pathogenic for humans or a particular animal species.

4.6 Obtaining scientific and medical consensus

Input from a range of disciplines (health, social, political and economic) is needed to establish a consensus about the potential impact from a pandemic virus, and benefits from different approaches to disease prevention and case management. Background data about the population structure will be needed, together with contact points within key organizations, and information relevant to the logistics of meeting a major medical and public health emergency. Some countries may wish to develop mathematical models that can be adapted quickly to actual situations. Examples of specific scenarios can be "tested" so as to evaluate possible outcomes with different approaches, such as when different amounts of vaccine are available, or vaccine is produced at different potencies to "stretch" supplies. Similarly, models can be developed for different morbidity and case-management scenarios. A bibliography of key reports and data sets should be assembled.

4.7 Ensuring pharmaceutical supplies and logistics

In recent years, new anti-viral agents to prevent or treat influenza infections have become available. Two drugs, amantadine and its derivative rimantadine, are now approved in several countries for use against influenza type A, which includes all the sub-types responsible for pandemics. Newer anti-viral drugs potentially effective against type B, as well as type A viruses, are being tested in clinical trials. Further information is provided about these drugs in Annex E.

Attention may be required to topics such as:

- Licensing procedures for new products in an emergency situation
- Planning the logistics for supplying influenza and pneumococcal vaccines, anti-viral drugs, antibiotics, masks, syringes, needles, etc.
- Estimation of the cost of such material, and expenses to cover their storage and transportation

http://www.unicef.org

http://www.ifrc.org

The UNICEF procurement program, and other multinational or national organizations experienced in provision of material for disaster relief or disease control operations (e.g., the International Federation of Red Cross and Red Crescent Societies, and other national and international aid, humanitarian and disaster relief organizations) could be contacted by those governments wanting assistance in making such estimates for their countries, using the normal channels that are already in place.

4.8 Legal-political-economic framework for action

Emergency actions to control the distribution of vaccine, or to reduce spread in the community, may require a legal basis, as well as needing wide political support. The costs of special measures will need to be approved, again possibly requiring special laws or political decisions. Steps should be taken to ensure that the necessary laws or regulations are in place in advance, and that methods to obtain political approval and financial support are understood. Estimated budgets should be prepared to guide the political decision-making process.

4.9 Communications

The threat of a pandemic of influenza will create a high demand for information, both from health professionals and the general public. A Pandemic Plan needs therefore to provide guidance about the approaches that will be most efficient and useful for communications about the threat and responses to it, presumably involving the national media, professional medical organizations, health authorities, and other parties. Plans will be needed to rapidly deal with false rumours and panic in a way that is credible with the general public.

TABLE 2: VIROLOGICAL/EPIDEMIOLOGICAL SCENARIOS*

	BEST CASE The new virus does not spread as much as in serious pandemics, or the illness caused overall is not very severe even in usually vulnerable groups		WORST CASE The new virus spreads rapidly and widely in the population, causing illness at least as severe as in most influenza A epidemics, with possibly extremely severe illness in some population groups	
OPTIONS	Advantages	Disadvantages	Advantages	Disadvantages
Option 1: No special vaccination program against the new virus	Considerable expenses are avoided.	Potential for the population to feel abandoned by their leaders in the early stages, when it is still unknown that the threat from the new virus is so limited.	Resources otherwise used for vaccination might be applied to strengthening health care delivery system to dealing with large numbers of severe cases. In planning a response, there is elimination of dependence on a product that might be unavailable in time.	Without benefit of vaccine, the morbidity and probably mortality is high. Strain on the health services is severe, with reduced staff and increased demand. National economy is seriously affected. Public fear and protest are likely. Possible disruption of civil order.
Option 2: Vaccinate selected groups, considered most important for health care, and overall infrastructure of the country. Perhaps 5-10% of the population would be targeted for vaccination.	The high costs and social upheaval associated with a large-scale vaccination program are avoided.	Potential criticism of process and decisions when identifying "most important" persons to be vaccinated. Those not selected for protection may feel left out by their authorities, even though no major disease occurs.	Disruption of vital community functions, including health care delivery, is minimized.	Impact of virus on most of the population remains severe, and many of the problems expected under Option 1 would still be expected to occur.
Option 3: Also attempt to vaccinate groups considered at high medical risk, (such as older persons, those with chronic underlying cardio-pulmonary disease, and possibly pregnant women or infants). Perhaps 25% of the population would be targeted for vaccination.	Program would be most consistent with normal influenza vaccination activities in many industrialized countries. Experience might enhance such programs in future years.	Unless extra funds are found the new vaccine will replace at least one component of the traditional one. High-risk populations may remain susceptible to illness if the new virus does NOT displace the old one. Interference would occur in the originally planned vaccine production.	Both the increase in demand for health care, and the difficulties in providing it, will be minimized. Overall, there should be a high cost-benefit for the vaccination program in terms of health care finances, and the impact on critical functions of society will be minimized.	The general population, including pre-school and school age children, and most working-age adults, will be seriously affected. Thus the national economy and many normal non-critical activities will be disrupted, with some of the other problems expected under Option 1 still likely.
Option 4: Attempt to vaccinate all (>90% of the population)	Experience in increasing supply and use of influenza vaccine. Should the new virus evolve into a more serious form, the population will have already been vaccinated.	Such a complicated program draws many resources away from other needs. Major controversy probable. Large-scale vaccination increases chances of adverse events that raise questions about vaccine safety.	To the extent vaccine supplies are available and used in time, the maximum reduction in impact of the pandemic virus would be obtained. National leaders would be acclaimed for their efforts.	Despite the overall benefits, there may be lack of understanding of the fact the vaccine is not 100% effective, and there will be situations where persons will claim they have been harmed by the vaccine.

* *The availability of vaccine is likely to be restricted, at least in the first calendar year after a pandemic virus begins to spread. Options may, therefore, need to be phased in as vaccine production increases.*

5 Issues on which national policy decisions will be needed

5.1 Management issues

- Which organizations in addition to the "permanent members" of the NPPC should be included in the planning process: physician organizations, pharmaceutical industry, veterinarians, businesses, educational and sport or other recreational organizations, religious and ethnic organizations, the military and law enforcement agencies, non-governmental voluntary organizations etc.?

- Is the process of preparing a plan, arranging for its review and if necessary taking responsibility for its implementation, to be directed by the government (e.g., Health Ministry or "civil defence" office) or outside of it (e.g., leading medical, public health or religious non-governmental organizations, or leading business/management experts)?

5.2 Surveillance issues

- Taking particularly into account the case definition that has been developed by WHO, what case definitions will be used in surveillance for a new virus sub-type?

- How can laboratory procedures recommended by WHO be implemented and how can their functioning be assured to provide early warning of a new virus sub-type as well as monitoring the impact during a pandemic?

- How many indices should be monitored, (e.g., number of encounters for influenza illness per GP, numbers of laboratory diagnoses, number of hospitalizations for pneumonia, mortality) and should they be only health-related or include other data such as absences from school or work, etc.?

- What sub-groupings will be needed for analysis, such as age groups, occupational groups, medical risk groups, etc.?

- What organizations should have contact points listed?

- What surveillance is needed about distribution, storage and use of vaccines, anti-influenza drugs, and antibiotics?

5.3 Scientific and medical issues

What may be the best options available from which to choose for disease prevention and management, and what are their advantages and disadvantages:

- Will there be special hazards for health and laboratory workers with a new virus sub-type?
- Will there be risks for wild or domestic animals in case of a cross-infection between a new human sub-type and animal species?
- What criteria in terms of occurrence, severity, and epidemic properties of a new sub-type will be used to initiate different levels of response?
- Taking into account the recommendations made by WHO, what populations would be expected target groups for vaccination, and would priorities be set in terms of vaccine use?
- Taking into account the recommendations made by WHO, what populations would be expected target groups for treatment with anti-viral drugs, and what priorities would govern their use?
- Taking into account the recommendations made by WHO, what vaccine doses and schedules would be recommended in the situation where a new virus sub-type had not replaced previously circulating strains?
- Are other measures appropriate to control spread or reduce impact on society, such as behaviour modifications including closing schools and limitations of indoor or outdoor public gatherings?
- Will hospitalizations be restricted to patients meeting strict criteria?
- Will cross training of staff in clinics and hospitals be needed to expand the supply of staff available for immunization programs or treatment of severely ill cases?
- What research should be undertaken?

5.4 Pharmaceutical supply and logistical issues

- What vaccines may be available at different time points during a pandemic, allowing for special difficulties of working with virus strains not previously seen in humans?

- If vaccines are needed from new manufacturing sources what steps exist to license them for use?

- What is the timetable for procuring and using vaccines, anti-viral agents and antibiotics?

- What ancillary supplies (masks, syringes, needles, respiratory therapy apparatus) may be required?

- What health care facilities (hospitals, beds, intensive care beds, and convalescence homes) and trained personnel will be available?

- Where could mass vaccination be undertaken, and at what rate?

- In case of high mortality how would corpses be stored, transported and buried or cremated?

- Is there a need for establishing strategic stockpiles of an anti-viral drug such as rimantadine, to have available at least for laboratory workers or medical staff at high risk of exposure to a new sub-type before vaccines against it can be manufactured? What are the procedures for using such a drug if it is not yet licensed in the country?

5.5 Legal-political-economic issues

- What laws and regulations enable or restrict government actions to respond to a public health emergency, such as establishing jurisdiction over vaccine supplies, assigning emergency staff, restricting hospital admissions, preventing public gatherings, etc.?

- Who will need to approve national policies that call for special expenditures, public health actions, control over operations of hospitals etc., and how should information be made available so as to obtain such approval?

- What overall costs are expected from a pandemic, and to enable different responses to it, including enhanced surveillance, monitoring, procurement of materials, etc.?

- What if any liability accrues to governments or health care providers for harm caused through emergency actions, including disrupting normal pharmaceutical manufacturing and sales (such as pre-placed orders for "normal" vaccine), unexpected vaccine reactions, cancelling major public gatherings such as concerts or sports events (if so recommended), imposing a quarantine or travel restrictions, or closing schools?

5.6 Communications issues

- Who will co-ordinate provision of information to the various sectors of society?

- What responses have been considered to reduce effects of rumours, or general panic?

- How will credibility be assured by official spokespersons?

- Is an electronic communication system in place to inter-connect different consultants, advisors, policy-makers etc. for planning meetings and discussion without constant travel?

6 Conclusions

Past influenza pandemics have occurred with little warning. In 1918, before laboratory diagnosis and characterization of viruses was possible, the only indications of a pandemic were the large increases in disease when a presumably dramatically different form of the influenza virus had already spread widely in different countries. Even in the pandemics that began in 1957 and 1968, when laboratory procedures were in place to study influenza viruses, relatively few samples were submitted to the single existing WHO reference centre, and there was no "early warning" about new sub-types of virus before outbreaks had already occurred in Asia.

In contrast, today:

See Annex F for address information

http://www.who.int/emc/diseases/flu/centres.html

- There are four WHO Collaborating Centres for Reference and Research on Influenza in different continents which each year characterize thousands of isolates;
- Among other countries that have joined the international surveillance program, China is an active participant;
- Methods for identifying new viruses include rapid genome sequencing;
- Communications about events, and transportation of laboratory samples, can be achieved rapidly;
- A large amount of knowledge exists about animal influenza viruses.

However, it has to be remembered that:

- Prediction of the onset of an influenza pandemic remains impossible;
- Preparation of control measures (such as manufacturing of a new vaccine) might take more time than is available before the pandemic strikes, and keeping stocks of anti-influenza drugs in amounts sufficient to treat whole population groups worldwide is unrealistic;
- Many countries lack sufficient resources to prepare appropriately for such an event;

- The increased volume and speed of international travel as well as the expansion of population in many regions and increased urbanization will put additional severe constraints on the establishment and implementation of efficient control measures.

Nevertheless, it is hoped that from these accomplishments the odds have been dramatically improved in favour of finding novel viruses before pandemics have begun, thereby increasing the time to organize a response, including production and distribution of vaccines.

However, as shown in Table 1, new sub-types of influenza viruses will occur without necessarily causing a pandemic. Hence pandemic planning must accomplish two objectives: effective assessment of risk from new viruses, and effective management of risk when the new viruses do indeed have properties enabling them to spread widely and cause serious disease.

Management of risk does not imply an ability to prevent a pandemic, but rather to make best use of available resources to reduce the extent of disease, reduce the impact of secondary catastrophies, and to prevent panic from occurring in the population.

In terms of risk assessment, we learnt in 1997 from the events in Hong Kong SAR (when a virulent avian influenza virus caused several severe infections in humans) that the ability to draw conclusions about the future impact of a new influenza sub-type might be hampered by the unexpected. Among the lessons learned are:

- National influenza centres need to be constantly alert for the existence of hard-to-identify viruses, and need to rapidly submit them with all information to one of the four WHO Collaborating Centres for Reference and Research on Influenza, so as to minimize time taken for their characterization

- Co-operation between veterinary, public health and biological regulatory authorities is needed to respond quickly to cases of apparent animal-to-human spread of a severe form of influenza of a novel sub-type

- Laboratories involved in influenza surveillance need to be equipped to handle a novel strain with due regard to prevention of infection of laboratory staff, and to prevention of release of the virus into the environment

- Non-traditional tests may be needed to confirm cases of infection with a new sub-type when reagents for traditional diagnostic methods are not readily available, or traditional tests do not work well

- A process involving continuous consultation among a wide variety of international experts is needed to evaluate laboratory and epidemiological data, when it is difficult to rapidly and reliably prove the lack of widespread person-to-person transmission of a novel sub-type.

In terms of managing the risk from a new virus, the situation in 1997 also indicated that assumptions about ability to make vaccine against a new virus must allow for the possibility of a strain that has biological properties which hinder the use of traditional vaccine production methods.

We must also recognize that no pandemic plan prepared in advance will be 100% relevant or best for whatever situation nature eventually creates. Hence emphasizing the process and the issues for responding to a possible or actual pandemic may be more important than specific details, which may prove inapplicable to a new situation. Accordingly, that approach has been used in developing the guidelines presented here.

Implementation of the response to a novel influenza must be highly credible, as resources will need to be rapidly diverted away from other efforts in order to focus on the threat. Hence, the appropriateness of responses should be reviewed continually by a group of knowledgeable persons who represent a broad range of interests, from governmental and non-governmental sources.

By encouraging national pandemic planning, WHO expects that important issues will emerge that will require continued international consultation to resolve. Examples of likely issues are differing policies in neighbouring countries, and inequity of vaccine availability between rich and poor countries. The exchange of national or regional pandemic preparedness plans is highly encouraged, in order to harmonize the response regionally.

Hence the process of advance preparation of national strategies is likely to be ongoing, requiring further involvement of WHO.

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7 Annex A: Influenza and its complications

Quick summary

Although in the large majority of cases influenza is an acute, self-limiting upper-respiratory infection, complications can occur. In epidemics and pandemics the overall attack rate is relatively high and occurs during a few weeks in any one location. Consequently, even a low frequency of complications results in measurable increases in rates of hospitalizations, and often in mortality. An important complication is involvement of the lower respiratory tract. This may occur from secondary bacterial, mixed viral-bacterial, or viral infections. Complications may also occur through exacerbation of pre-existing chronic disease, particularly cardio-pulmonary disease. Cardiac complications have also been observed in healthy young adults. Young infants and pregnant women appear to be at risk of increased hospitalization from influenza, as do other persons of any age whose ability to cope with a chronic condition is compromised by influenza infection. Usually the most serious consequences are seen to increase with age, particularly above about 65 years.

Analysis of hospital records and mortality statistics over many years provides evidence of the role of influenza as the primary cause of serious complications in both previously healthy persons and those with prior underlying conditions (Collins, 1953; Glezen, 1987). In addition, detailed studies of collections of individual cases identify rare symptoms or sequelae believed associated with influenza infections. Brief descriptions of the more important or challenging ones are provided below.

Pulmonary complications

Croup, exacerbation of chronic obstructive pulmonary disease (chronic bronchitis, asthma and cystic fibrosis), and pneumonia are all recognized with influenza infections. The most life-threatening of these is pneumonia (Kaye, 1961; Martin, 1959; Stuart-Harris, 1966); three types of complicating pneumonia have been described:

Bacterial pneumonia (most common)

This may occur in previously healthy persons after influenza virus has damaged the epithelium in the airways, as well as in those with underlying disease rendering them more susceptible to bacterial infections. Secondary bacterial infection should be strongly considered in patients who report a severe fever or the reappearance of fever or other symptoms of bacterial infection in the respiratory tract after their initial influenza illness has improved.

Combined viral and bacterial pneumonia (less common)

Current pathogenesis studies are wondering how much of "bacterial" is in combined viral and bacterial pneumonia. It may be more common than pneumonia due to a single agent (Scheiblauer, 1992), particularly in patients with chronic cardiovascular and pulmonary diseases.

Pure viral pneumonia (rare)

Primary viral influenza pneumonia is the least common of the pulmonary complications (Burk, 1971).

Pneumonia secondary to influenza leads to pleuritic pain, sometimes with evidence of consolidation and pleural effusions (Burk, 1971). However, clinical signs and symptoms can be very atypical in the elderly. If not resolved, death may result from asphyxia, sepsis and toxic shock syndrome (Martin, 1959; Sperber, 1987), or cardiac arrhythmias (Martin, 1959). Rapid progression over the first few days, after onset of high fever, and cough to severe dyspnea, and cyanosis are consistent with a diagnosis of severe influenza virus pneumonia. Physical examination and chest x-ray often reveal bilateral changes sometimes with signs of consolidation. Gram stains of sputum may show no evidence of bacterial pathogens, and few polymorphonuclear leucocytes, while blood gas studies show hypoxia. Lack of response to therapy for cardiac pulmonary oedema (Kaye, 1961), and congestive heart failure may occur in persons with underlying heart disease (Schwarzmann, 1971).

In any patient with pneumonia, antibiotic therapy is normally indicated without waiting for laboratory confirmation of a bacterial cause (Martin, 1959; Jones 1991). Current susceptibility/resistance patterns should be considered for decisions on specific antibiotics. The most common bacterial pathogens are *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Haemophilus influenzae* (LaForce, 1994; Scheiblauer, 1992). Failure to achieve a satisfactory therapeutic response may be due to antibiotic resistance, to circulatory failure or to the overwhelming toxic effects of the infection in patients with existing chronic lung or heart disease (Stuart-Harris, 1966). Supportive care to treat the acute respiratory insufficiency should be available. Treatment of the viral component of pneumonia is not an established practice. In some locations ribavirin small particle aerosol therapy might be considered.

Non-pulmonary complications

Cardiac complications

The most common cardiac complication is atrial fibrillation, particularly in older persons. It may indicate the presence of ischaemic heart disease (Stuart-Harris, 1966). ECG changes during acute influenza are noted in patients who have cardiac disease but these have been ascribed to exacerbation of the underlying cardiac disease rather than to direct involvement of the myocardium with influenza virus (Dolin, 1991). Left or right heart failure may also occur (Stuart-Harris, 1966). Myocarditis and

pericarditis, while difficult to prove by laboratory methods to result from influenza virus, are believed to occur in rare cases and may be fatal (Martin, 1959).

Ryositis and rhabdomyolysis

Involvement of muscles has been reported most commonly after influenza B infection of children. Leg pains and muscle tenderness last for 1-5 days (Middleton, 1970). Serum CPK levels are elevated, and acute myoglobinuria may result in acute renal failure due to tubular necrosis. Specific treatment may be necessary (Leebeek, 1995; Simon, 1970).

Central nervous system complications

Transverse myelitis and encephalitis occur rarely. Mania and schizophrenia were associated with the 1918 pandemic.

Reye's syndrome

This is a rare hepatic and central nervous system complication seen after viral infections, in particular influenza B, almost exclusively occurring in children, and linked with use of salicylates. Symptoms are a change in mental status, nausea and vomiting due to oedema of the brain. Treatment is general supportive measures, intubation and reducing intracranial pressure (Dolin, 1991; LaForce, 1994).

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8 Annex B: Historical background

Quick summary

The history of previous pandemics and pandemic threats shows that new sub-types of influenza A virus do not appear at defined intervals (as was once believed), and all occurrences of human infection with a novel sub-type of influenza A virus cannot be expected to lead to a pandemic. When true pandemic viruses do appear, there may be several waves of outbreaks with an interval of 6-9 months in between before the full impact of the new virus is felt. This suggests that prevention programs involving vaccines or anti-viral drugs could be more widely in place for such second waves than for the first. However, planning for pandemics should take account of the possibility for very rapid dissemination of a true pandemic virus from its initial focus of activity, due to increased international travel.

Pandemics have affected different segments of the population with differing levels of impact. The most benign pandemic was when type A(H1N1) viruses from 1950 re-appeared for unknown reasons in 1977, and affected mainly infants and children. Mortality did not increase. In 1918, when mortality was estimated at >20 million worldwide, adults (e.g., 20-50 years old) were extremely seriously affected. Pandemics in 1957 and 1968 affected all ages, with greatest excess rates of mortality in the >65 year old population, and in persons of other age groups who had underlying medical conditions.

Influenza-like disease was well described by Hippocrates in 412 BC, and influenza-like outbreaks since 1173 AD were clearly tabulated by Hirsch (Hirsch, 1883). The first well-described pandemic of influenza-like disease occurred in 1580, and since this period, 31 possible influenza pandemics have been documented (Noble, 1982). In 1918-20, a pandemic occurred that is renowned for its severity, being held responsible for 20 to 40 million deaths in the world (Ghendon, 1994; Marwick, 1996). The overall clinical attack rate was as high as 40%, and severe forms of pneumonia were common. It seems highly likely, based on observations in subsequent pandemics, that the actual infection rate was even higher. Particularly noteworthy was that the attack rate and mortality were generally highest in 20-50 year old adults (de Gooier, 1978). At the time, laboratory methods did not exist to identify the causative agent. Convincing data, obtained later, however, showed that the pandemic was caused by a type A(H1N1) influenza virus closely related to viruses that can be still be found in pigs in some countries (Taubenberger, 1997).

Since then, three more pandemics have occurred: "Asian 'flu" due to type A(H2N2) virus, beginning in 1957; "Hong Kong 'flu" due to type A(H3N2) virus, beginning in 1968; and "Russian 'flu" due to type A(H1N1) virus, beginning in 1977. During the "Asian" and "Hong Kong" pandemics, all age groups were susceptible. Mortality rates increased, particularly for those >65 years old. Excess mortality was also observed for those with underlying medical risk factors, such as cardio-pulmonary disease. However, generally healthy young adults were much less severely affected than in 1918. Also, in 1957, the H2N2 virus completely replaced the previous H1N1 virus, and, in 1968, the H3N2 virus replaced it in turn.

The 1977 pandemic was quite different from the previous ones. For unknown reasons the causative virus appeared to represent the reappearance of a form of the H1N1 virus last seen during epidemics in about 1950. Consequently, those born before about 1957, in the era of circulation of type A(H1N1) viruses, were on the whole protected against infection or serious illness by the H1N1 virus which reappeared in 1977/78. Thus, nearly all reports from 1977/78 indicate that adults were minimally affected, whereas outbreaks of typical influenza illness, with high attack rates, occurred in school and college age children and youths. This profile changed to all age groups in subsequent years. Furthermore, unlike in 1957 and 1968, the new sub-type did not replace the previously circulating one. Thus, type A(H1N1) viruses which evolved from the 1977 strain have by now co-circulated for more than 20 years with type A(H3N2) viruses derived from the original 1968 pandemic strain, which still cause epidemics.

Pandemic planning must take into account not only the history to be learnt from true pandemics, but also the events following the appearance of new strains that did NOT cause pandemics. The most important examples of this have been in February 1976 in the US, and in May-December, 1997, in Hong Kong SAR. In the former case, a type A(H1N1) virus related to swine influenza was isolated from an Army recruit who subsequently died. The virus had limited local spread among recruits within the same camp. These events set in motion a pre-emptive campaign to produce and vaccinate as many as possible of the US population before the next winter 'flu' season. Indeed, about 40 million people were vaccinated by the end of 1976. However, the program was stopped because it was evident by then that the virus was not spreading, and also there were concerns about rare but serious complications from the vaccine (Dowdle, 1997; Stuart-Harris, 1985). Two other non-pandemic new strains were also identified in 1986 (de Jong, 1988) and in 1988 (Wells, 1991).

The more recent "false alarm" in Hong Kong SAR began with a single sporadic (but fatal) infection of a child in May 1997. An influenza A virus was grown, but could not be sub-typed locally. Some time later the virus was determined to be closely related to type A influenza of avian origin, with the sub-type H5N1. No previous human infections with this sub-type had been proven. Beginning in about November, a series of 17 further cases of infection, with closely related virus, was detected in Hong Kong SAR. Many cases were severe, particularly in adults, of whom 5 additional subjects died. The simultaneous occurrence of outbreaks of H5N1 virus in chickens grown or imported into Hong Kong SAR for food suggested these birds were the actual source of human infection. Intense investigations of contacts have failed to produce a better hypothesis, since most of the infections did not seem to transmit well from person-to-person, and further cases in humans ceased in parallel with the mass slaughter of chickens in Hong Kong SAR by the veterinary authorities.

Two influenza A(H9N2) viruses were identified in April 1999 in two hospitalized children, ages 1 and 4 years, in Hong Kong SAR. Analysis of specimens showed that the two viruses were similar to the influenza A/QUAIL/HONG KONG/G1/97 virus; the internal genes were also simiar to the internal genes of 1997 isolates of human and chicken H5N1 viruses. Both cases showed mild symptoms and have all recovered. Both were small children.

These three experiences have changed thinking about the origin of pandemics. First, it is now clear that there is no predictable time frame or "cycle" after which a pandemic will occur. Previously, based on incomplete knowledge of the nature of virus strains causing major epidemics in 1946/47, there had been almost a "dogma" that pandemics occurred at about 11 year intervals. As discussed above, however, type A(H3N2) viruses have now circulated for >30 years since the pandemic in 1968. Secondly, the occurrence of human cases of infection with a virus of novel sub-type did NOT lead to pandemic spread on at least two occasions. Hence, it must be recognized that viral properties other than antigenic sub-type are important in determining a virus' ability to spread. The unpredictability of influenza, and the serious consequences which can occur when a pandemic strain does appear, provide an ample justification for constant vigilance, and good planning, to improve preparedness, if another true pandemic virus does appear.

The time from the first recognition of a new sub-type and the onset of a full-blown pandemic may be too short to prepare a vaccine and use it. Even so, all the time gained from advance planning should be of value in managing the threat. Pauses in the spread of the virus can occur which provide time for progressive implementation of prevention activities as the pandemic proceeds. For example, in 1918, two intervals of 3 months occurred between each of three pandemic waves in Belgium (Collard, 1974); similarly, during the 1968 pandemic in Great Britain, the epidemic virus initially was observed only in one family and a school during August - September 1968, but the attack rate gradually increased in January and March 1969, and a sharp second wave occurred, several months later with mortality peaking in December 1969 (Stuart-Harris, 1970). Thus, 18 months passed between the isolation of the virus in Hong Kong SAR and aggressive outbreaks in Europe.

However, current concerns about a future pandemic include the fact that the advent of air travel may hasten the spread of new epidemic strains. For example, it is suggested that the spread of Hong Kong virus in 1968 was faster than the spread of virus in 1918 (Hannoun, 1995). Furthermore, in 1977, the type A(H1N1) virus seen in early winter outbreaks in China and Siberian areas of Russia reached the rest of the Northern Hemisphere during the same winter, and caused epidemics in the Southern Hemisphere immediately thereafter.

TABLE 3: INFLUENZA LANDMARKS IN HUMANS IN THIS CENTURY

YEAR	COLLOQUIAL NAME AND SUBTYPE	SOURCE	IMPACT	
1918	"Spanish ' flu" (H1N1 viruses like "Swine ' flu")	Possibly emergence from swine or an avian host of a mutated H1N1 virus	Pandemic with >20 million deaths globally	PANDEMICS
1957	"Asian ' flu " (H2N2)	Possibly mixed infection of an animal with human H1N1 and avian H2N2 virus strains in Asia	Substantial pandemic H1N1 virus disappeared	
1968	"Hong Kong ' flu" (H3N2)	High probability of mixed infection of an animal with human H2N2 and avian H3Nx virus strains in Asia	Substantial pandemic H2N2 virus disappeared	
1977	"Russian ' flu" (H1N1)	Source unknown, but virus is almost identical to human epidemic strains from 1950. Reappearance detected at almost the same time in China and Siberia	Benign pandemic, primarily involving persons born after the 1950s. H1N1 virus has co-circulated with H3N2 virus in humans since 1977	
1976	"Swine ' flu" (H1N1)	US/New Jersey. Virus enzootic in US swine herds since at least 1930	Localized outbreak in military training camp, with one fatal case	SOME INCIDENTS WITH LIMITED SPREAD IN HUMANS
1986	H1N1	The Netherlands. Swine virus derived from avian source	One adult with severe pneumonia	
1988	"Swine ' flu" (H1N1)	US/Wisconsin. Swine virus	Pregnant woman died after exposure to sick pig	
1993	H3N2	The Netherlands. Swine reassortant between "old" human H3N2 (1973/75-like) and avian H1N1	2 children with mild disease. Father infected by pigs suspected to be the transmitters	
1995	H7N7	United Kingdom. Duck virus	One adult with conjunctivitis	
1997	"Chicken ' flu" (H5N1)	Hong Kong SAR. Poultry	18 confirmed human cases, 6 lethal	
1999	H9N2	China, Hong Kong SAR. Quail influenza-like virus	2 human cases with mild disease	

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9 Annex C: Origin of pandemics

Quick summary

There are three theories for the emergence of pandemic viruses: genetic reassortment between human and animal viruses, direct transfer of viruses between animals and humans, and re-emergence of viruses from unrecognized or unsuspected reservoirs. Genetic reassortment is a likely explanation, for example, as to how type A(H3N2) viruses arose in 1968 that had acquired a new haemagglutinin gene compared to the predecessor H2N2 Asian influenza viruses. Reassortment could possibly occur by mixed infection in swine, which can be susceptible to viruses from avian and human sources. Agricultural practices and ecological circumstances in China and in other comparable locations may provide ideal opportunities for such co-infections to occur. The second theory is the most likely explanation for the 1918 pandemic virus. The third theory has been advanced to explain the reappearance of H1N1 virus in 1977 that resembled virus from 1950, although it is not currently understood where and how any influenza virus could remain unrecognized for many years.

The causative agent of influenza has been known since 1933, and influenza viruses are now classified into two main types, A and B. Although influenza A and B viruses regularly give rise to epidemics, only the influenza A virus has shown the ability to cause pandemics. During non-pandemic periods, the influenza A and B viruses evolve by accumulating mutations in the haemagglutinin (HA) and neuraminidase (NA) proteins. These changes are called 'antigenic drift' and a new epidemic strain typically differs by a small number of amino acids in the HA protein (Schild, 1996). Pandemic viruses appear by 'antigenic shift', which is characterized by a dramatic change in the HA sub-type, with or without a change in the NA.

There are three theories for the emergence of pandemic viruses:

- genetic reassortment occurring in humans or between human and animal viruses
- direct transfer of viruses between animals and humans
- re-emergence of viruses from unrecognized or unsuspected reservoirs

The first theory is based on the fact that both the type A(H2N2) pandemic strain from 1957 and the type A(H3N2) pandemic strain from 1968 contained genes derived from avian influenza viruses and human viruses (Webster, 1992). Indeed, the main difference between these two viruses is the substitution of the gene coding for the haemagglutinin in 1968, changing it from H2 to H3. Due to the segmented nature of the influenza viral genome, genetic reassortment readily occurs during mixed infections. It is thought that reassortment between avian and human viruses

could take place in pigs, which appear susceptible to infections with some influenza viruses of human and avian origin (Scholtissek, 1987).

Historical records suggest that pandemic strains first appeared in China in the 1957, 1968 and 1977 pandemics. China has a large population and many communities practice both pig and duck farming. Also, there is wide climatic variation from North China to South China, so that influenza infections of humans occur normally every month of the year somewhere in this single country. This combination of factors could be the key to the origin of influenza pandemics. Thus, it is possible that the agricultural practices and ecological circumstances in this area provide continual opportunities for the co-infection of animals to occur with human, avian and swine influenza viruses. Such co-infections would enable reassortants to arise, from which those with human epidemic properties could then be selected through a series of transmissions between animals or humans over an extended period of time. However, locations other than China exist where close contact between species, including humans, enables reassortant influenza viruses to arise that can infect humans, as suggested by the isolation of avian-human influenza A(H3N2) reassortant viruses from children in the Netherlands (Claas, 1994).

The second theory is best supported by genetic evidence that nucleic acid found in tissues preserved from victims of the 1918 pandemic are closely related to genes of early swine H1N1 viruses (Taubenberger, 1997). Swine influenza viruses themselves appear quite closely related to avian influenza viruses (Webster, 1992). If this were so, then the combination of evidence again would suggest an importance for avian species as a reservoir of influenza virus genes capable of contributing to human pandemic strains. The possibility for direct transfer of avian viruses to humans, without reassortment, was confirmed when pathogenic avian influenza A(H5N1) virus caused a limited number of infections, but some with serious illness and death, in residents of Hong Kong SAR in 1997 (WHO, 1998). Other examples of apparent direct transmission of influenza virus from bird to human are the isolation of avian influenza A(H7N7) from an adult in England (Kurtz, 1996) and influenza A (H9N2) in 2 cases in Hong Kong SAR (1999). Person-to-person transmission was not found.

Superimposed on both the above theories is the possibility that only certain HA sub-types (i.e., H1, H2, H3) have epidemic potential in humans, and that these will recycle in humans in some manner. Such a theory is based on studies of antibodies in sera from people alive during earlier pandemic periods. This serologic data suggests that the pandemic virus in 1889 had an H2 haemagglutinin, related to that found in the 1957 pandemic virus, and that the pandemic virus in about 1900 had an H3 haemagglutinin related to that found in the 1968 pandemic virus. Similarly, the type A(H1N1) virus, which reappeared in 1977, had both haemagglutinin and neuraminidase genes (as well as all other genes) essentially the same as found in H1N1 virus from 1950. If this theory of limitation on the sub-types capable of infecting and transmitting in humans is true, it is not known whether these sub-types can be maintained for 20-80 years between pandemics only in the form of animal influenza viruses, or in some other way. It is certainly difficult to explain the close overall similarity between the 1977 and 1950 type A(H1N1) viruses without invoking "dormancy", which therefore should be considered, in theory, as a third possible mechanism for emergence of pandemic influenza viruses, despite the lack of knowledge of how influenza virus could remain hidden for many years.

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10 Annex D: Influenza vaccine

Quick summary

Influenza virus vaccines are normally made by growing approved seed viruses in embryonated chicken eggs, purifying and chemically treating the harvest, including inactivating infectivity, and then adjusting the concentration against reference biological standards. In the case of a pandemic virus, however, special issues arise concerning vaccine composition and packaging that must be addressed before vaccine production can be completed. The lead-time from identifying a new strain to beginning vaccine production is usually 2-3 months, and vaccine lots first become available within about 4-5 months of inoculation of eggs. Thus, in the face of a pandemic threat, an expected minimum 8 months will pass before new vaccine first begins to be distributed from manufacturers. Live attenuated influenza vaccines exist which are presently used in one country, and are approaching the point of licensure in another. There is less experience at this point to predict the minimum time before distribution of a new live vaccine strain could begin, although in theory it should be similar to that of traditional killed vaccine. Early consideration of various issues could reduce somewhat the delays between the identification of a possible pandemic virus and the supply of vaccine becoming available for use.

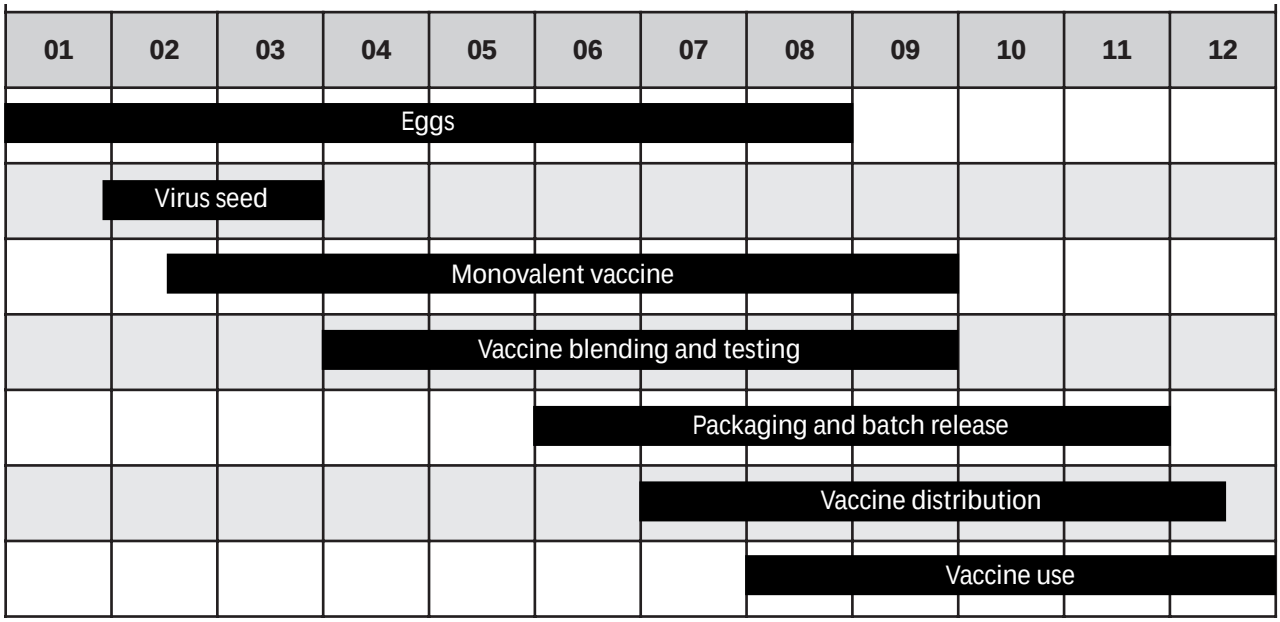
Influenza epidemics usually peak between December and March in the Northern Hemisphere, and during June-September in the Southern Hemisphere. To allow for the production of vaccines to be used before the winter season, a WHO meeting to select strains for vaccines takes place in February each year for the Northern Hemisphere, and in September for the Southern Hemisphere.

The key steps in the production of inactivated influenza vaccines are illustrated below. In some cases, newly recommended strains do not grow well in the embryonated chicken eggs used for vaccine production, so "high growth reassortant viruses" (hgr viruses) must be made. During inter-pandemic times and once the WHO recommendation has been made, vaccine production processes can actually begin immediately, if the vaccine is multivalent and contains at least one previously used strain. Development of seeds suitable for production of new strains can be completed during this same time period. However, in a pandemic situation, it is likely that monovalent vaccine would be made; in this case, efforts to reduce time for development of seed viruses would be desirable, since all other activities must await this phase to be completed.

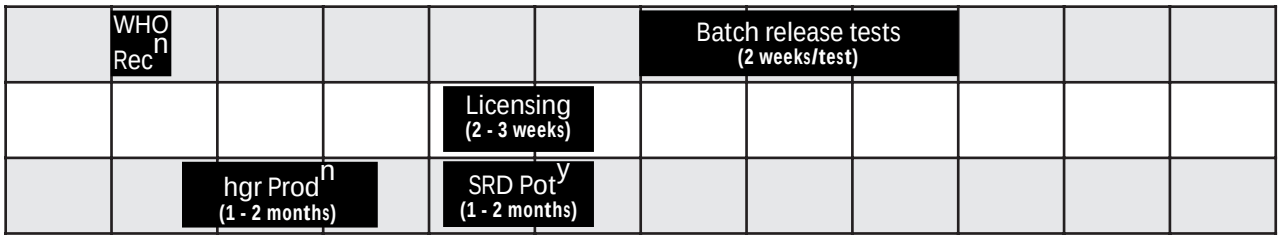
Reagents for vaccine standardization are produced at the Center for Biologics Evaluation and Research (CBER), USA; National Institute for Biological Standards and Control (NIBSC), UK; and the Therapeutic Goods Administration (TGA), Australia. These comprise sheep antiserum and calibrated antigen for use in the single-radial-diffusion (SRD) test. About 2-3 months are needed to prepare these reagents from the time each new strain is recommended, possibly adding a further important delay when only monovalent vaccines to a pandemic strain will be manufactured. Once SRD reagents have been received, manufacturers can standardize the potency

of each monovalent vaccine batch, and then in normal years blend the vaccines into a multivalent final product. At present three strains are used, type A(H3N2), type A(H1N1) and type B, at the required doses of 15 μg HA. Because each year's vaccines are made by the same process, many countries use a re-licensing procedure to approve the current year's new strain(s). This may involve official batch release testing by multiple countries of either monovalent vaccine or final lots of multivalent product, which can take up to 2 weeks per batch. Thus the whole process from identification of a new strain to first availability of vaccine usually takes no less than about 8 months.

TABLE 4: Timetable in months for Northern Hemisphere influenza vaccine production during the inter-pandemic period



Key events



Abbreviations:

Rec^{n} - WHO Recommendation of vaccine strains

hgr Prod^{n} - Production of high growth reassortants

SRD Pot^{y} - Production of single-radial-diffusion potency reagents

Reducing the production time of vaccines

- Early preparation of vaccine production seeds

  If possible, production seeds ("reassortants") should be developed for killed and live attenuated vaccines (where licensed) as soon as pandemic viruses are detected, and in advance of deciding whether they are needed. Under optimal circumstances this might be done in as little as 3-4 weeks. However, the H5N1 virus isolated from cases in Hong Kong SAR in 1997 created several unanticipated difficulties because of its pathogenicity for chickens and embryonated chicken eggs, as well as the high case-fatality rate among infected people in Hong Kong SAR. There was therefore a need for laboratories receiving the original isolates to have approved biological containment facilities and procedures, which would protect laboratory workers and prevent any possible release of the virus into the environment. Contingency planning for future pandemic threats should take measures to ensure that the necessary laboratory facilities and procedures exist in numerous sites, including those involved in developing vaccine seeds or manufacturing processes.

- Early preparation of vaccine potency testing reagents, or other time-saving approaches

  Normally, 4-8 weeks are needed to produce SRD reagents for standardizing killed influenza virus vaccines. It may be possible to reduce this time to one week if SRD reagents to potential pandemic strains are stockpiled, for example, reference strains for all haemagglutinin sub-types. An alternative would be to attain consensus that would allow different potency tests to be used. One possibility, in this regard, might be the determination of the amount of viral haemagglutinin by procedures, which do not use sub-type specific immunological reagents.

- Reduce delays in licensing of vaccines

  At present more than one national control authority may be involved in approving the release of vaccine, since vaccines are used in many countries. Agreements on centrally licensing vaccines for distribution in multiple countries could overcome this problem.

- Develop alternative production procedures

  Orders for eggs to produce vaccines by current technology must be made at least 6 months in advance of production beginning. This may cause difficulties if a pandemic virus emerges outside the normal time when vaccine production is planned. Alternative methods of production, based on fermentation technology such as virus growth in tissue culture or antigen production by recombinant DNA technology, should be pursued.

• Establish a research agenda

It is possible that other approaches to vaccination may improve their effectiveness. Live attenuated vaccines already offer the potential to immunize with a single dose those who have never experienced the antigens contained in the vaccine. This would appear to be a potentially important advantage in a pandemic, but needs further consideration and research, including addressing any special concerns arising from the introduction of a new haemagglutinin sub-type in an infectious influenza vaccine during a pre-pandemic period. Mixing traditional vaccines with adjuvants may improve immunogenicity, and again could eliminate the need for two doses in unprimed populations, and possibly also reduce the amount of antigen needed for each dose, thereby expanding supplies.

DNA vaccines represent another possibility that could provide large numbers of doses in a short time. As it is not known when the next pandemic will take place, intensive research on the above may considerably improve the approaches available by then.

Vaccine valency

• Standardize pandemic virus vaccine to be monovalent

Since 1977, WHO has recommended that influenza vaccines be trivalent, containing one type A(H3N2) virus, one type A(H1N1) virus and one type B virus. When responding to a pandemic threat, decisions must be taken whether the pandemic virus vaccine will be used alone, or in combination with one or more other viruses, in case these do not disappear. This will depend on surveillance results and best judgement at the time. If it is felt necessary for WHO or individual countries to recommend multivalent vaccines, due to uncertainty about the disappearance of former strains, this will likely reduce the total supply of vaccines against the pandemic virus and complicate the international sharing of vaccines.

Purchasing and distribution

• Plan for emergencies when negotiating vaccine procurement contracts

Many national governments, and major pharmaceutical distributors, have yearly contracts with manufacturers for influenza vaccines. In the event of a pandemic, those vaccines may prove unneeded, even though manufacturers may have begun or completed their production. Each vaccine manufacturer should discuss with the country(ies) where the influenza vaccine is usually produced or distributed, how such contingencies can be addressed, and, in an emergency, what can be the expected rate of production, i.e., the number of doses / month from the time they receive the seed strain of a pandemic virus. Production targets may depend

on the type of packaging (single dose or multi-dose vials) desired, whether split vaccines or whole virus vaccines will be produced, and the potency of the vaccine. In preparing for a pandemic it may be desirable to build flexibility into procurement procedures, to allow for different vaccination strategies. Thus, a decision might be made in advance to have contracts permitting the emergency production of multi-dose vials of vaccine containing 7 micrograms per dose instead of the usual 15 micrograms, to allow for stretching supplies or for a schedule of two 7 microgram doses instead of one dose of 15 micrograms in order to maximize immune response in populations lacking prior exposure to an antigen related to that of the pandemic strain.

- Explore possibilities for a "clearing house" to balance purchases and deliveries versus supply

  Each government and vaccine supplier will need to consider how much vaccine they will guarantee to purchase or sell in an emergency situation. The cost per dose may be different if vaccine is being purchased by governments and made available to recipients without cost, or if vaccine is to be purchased at the user's expense. Without a "clearing house" to balance demand and supply, cost considerations rather than public health may drive vaccine distribution needs. The needs of non-industrialized countries without any resources to purchase vaccines may be completely overlooked. A mechanism such as a central clearing house, operated and funded by a number of co-operating countries, might allow for vaccine purchases to be "pooled" and distributed more equitably than otherwise. Such a system could also ensure that a portion of vaccines is purchased as a humanitarian donation for use by designated population sectors in non-industrialized countries, such as health care workers, pregnant women or others with high risk of exposure and severe disease who play essential long-term roles in society.

- Design approaches to vaccine distribution that will be appropriate for an emergency situation

  Different countries have different systems by which vaccine reaches those to be immunized. These procedures may need modification if faced by a pandemic. Determinations will be needed whether vaccine distribution will proceed only from facilities under direct jurisdiction of government employees, or through private distribution channels. Potential problems in ensuring vaccine security and accountability need to be considered, including manufacturers and distributors in the process. Timely and up-to-date statistics on vaccination supplies and use will be needed to guide those distributing a product that would be expected to be in high demand and short supply. Surveillance for, and interdiction of, stolen and counterfeit vaccines is likely to be a new problem.

- Establish international co-operation for assessing safety of influenza vaccines

  Considerable problems can develop if either inappropriate reports are publicized about vaccine-related serious side effects, or failure to detect true risks from a new vaccine that would be widely used over a short period of time. As information travels rapidly over the Internet and through other channels, international co-operation would appear highly desirable to share experiences and assist in ensuring truthful reporting of events.

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11 Annex E: Anti-viral drugs

Quick summary

In vitro test results of the anti-influenza drug amantadine with human and most avian influenza virus sub-types indicate that any future pandemic strain would also be sensitive to this drug and its derivative rimantadine (Oxford, 1996). These compounds have been shown to be clinically effective in preventing illness, when taken throughout the period of exposure to virus in a normal epidemic or outbreak situation. They also can reduce the severity and duration of illness, when taken early after onset. In the latter situation, they may select for resistant variants, which can spread to close contacts but are unlikely to spread further.

Other anti-influenza drugs with a different mode of action to amantadine and rimantadine appear promising in laboratory and clinical trials. However, policies are needed about the roles of these drugs in a pandemic situation, when they may for a time be the only specific measures with which to combat a new virus. Cost and supply problems make it unrealistic to consider them for widespread prophylactic use.

Nevertheless, as part of pandemic planning, it would be appropriate, as a precaution, to ensure that mechanisms exist to import, license and use those drugs already approved in some countries, and to maintain a supply adequate for critical needs which might arise, such as protection of health care staff and laboratory workers who may be exposed to a new virus. Of the two currently used drugs, rimantadine has the better safety profile.

The availability of anti-viral drugs will normally precede the availability of vaccine to a new strain. Nevertheless, issues related to anti-viral drugs are similar to those for vaccines: target groups and equity of distribution, dose, availability, (im)possibility to respond to a sudden increase of demand, and safety.

Currently there are two anti-influenza drugs that are licensed in some countries: amantadine and rimantadine. Their effectiveness is similar, but rimantadine has a better record of safety. Specifically, amantadine is excreted renally, and can cause significant neurological side effects, particularly in those with diminished kidney function, including generally healthy elderly persons. This does not appear to be a problem for rimantadine.

Both drugs interfere with the replicative cycle of influenza A but not B viruses, through blocking the function of a membrane spanning protein synthesized in influenza-infected cells. Each has been found to be >70% effective in preventing illness caused by influenza A virus (Dolin, 1982).

WHO recommends either drug for use in the elderly and high risk people, when influenza A viruses threaten high risk residents of institutions, and vaccine is not yet available or has only just been administered (WHO, 1985).

The recommended dose of amantadine for prophylaxis and therapy is:

200 mg daily for adults

100 mg for 10-15 years and over 65 years

2-4 mg/kg for children 1-9 years

Doses must also be reduced in case of decreased renal function. Occasional resistance to amantadine and rimantadine can develop in viruses present in persons using the drugs to treat symptoms (Belshe, 1989), and such drug-resistant viruses may be transmitted to contacts (Hayden, 1989). The long-term epidemiological significance of drug-resistant viruses is not yet known, but no rationale or evidence has been found as to why such resistant mutants would have a biological advantage and spread.

Recently two closely related compounds have been developed that bind to the active site in a minor protein found on the surface of influenza viruses, the enzyme neuraminidase. The binding appears extremely strong, and, in laboratory tests and human clinical studies, inhibits virus replication to a high degree, and provides protection similar to amantadine and rimantadine. Resistance may be less frequent than with amantadine and rimantadine. Presently, the compounds are undergoing large-scale human clinical trials to support applications for licensure. If approved, and found to have a good safety profile, either drug would offer the advantage, during inter-pandemic situations, of being useful regardless of the virus type. Having anti-influenza drugs available, which act on different viral targets, may permit application with less concern about resistance, and possibly will provide opportunities for use in situations such as the early stages of primary viral pneumonia.

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12 Annex F: List of addresses

For National Influenza Centres and WHO Collaborating Centres for Reference and Research on Influenza see also: http://www.who.int/emc/diseases/flu/centres.html

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Fax: 021 613 989

Influenza Vaccine Manufacturers

For Influenza Vaccine Manufacturers, see also: http://www.who.int/emc/diseases/flu/manuf.html

Austria:

Immuno AG
Uferstrasse 15
A-2304 Orth/Donau, Austria
Tel +43-2212-2701 314
Fax +43-2212-2716

Australia:

CSL Limited
45 Poplar Road
Parkville, Victoria 3052, Australia
Tel +61-3-93 89 12 72
Fax +61-3-93 89 18 87

Belgium:

SmithKline Beecham
Rue de l'Institut 89
B-1330 Rixensart, Belgium
Tel +32-26 56 87 71
Fax +32-26 56 91 32

Canada:

Biochem Vaccines Inc.
(A subsidiary of Biochem Pharma Inc.)
2323 Parc Technologique
Sainte Foy
Quebec G1P 4RS
Tel +1-418-650 00 10
Fax +1-418-650 00 80

France:

Pasteur-Merieux Serums et Vaccins
58 Avenue Leclerc
F-69007 Lyon
Tel +33-04 72 73 77 07
Fax +33-04 72 73 77 37

Germany:

Sächsiche Serumwerk GmbH
Zirkusstrasse 40
D-01069 Dresden
Tel +49-351-456 12 28
Fax +49-351-456 12 11

Behringwerke AG
Postfach 1140
D-3500 Marburg (Lahn) 1
Tel +49-6421-39 24 71
Fax +49-6421-39 47 94

Italy:

Istituto Siero Vaccinogeno Italiano SPA
227 bis km 19.5
I-80029 Sant Antimo
Naples

Chiron Biocine
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Tel +39-577-24 31 11
Fax +39-577-24 30 74

Istituto Vaccinogeno Pozzi SPA
Via Cassia Nord
La Tognazza 21B
I-53100 Siena 53100

Japan:

Denka Seiken Co. Ltd
Taiyo bldg
12-1 Kabuto-chu, Nihonbashi, Chuo-ku
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Tel +81-3-3669 9091
Fax+81-3-3664 1005

Chemo-Sero-Theraputic Resaerch Institute
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Telex: KUMAMOTO KAKETSUKEN CSTI J

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Fax +81-6-876 1984
telex: BIKEN-ZAIDAN SUITA JAPAN

Korea, Republic of:

Dong Shin Pharmaceutical Co, Ltd
994-3 Daechi-dong, Kangnam-ku
Seoul
Tel +82-2-556 99 66
Fax +82-2-557 88 98
telex: 27579 VITAPHA

Netherlands:

Solvay Pharmaceuticals BV
C. J.van Houtenlaan 36
P.O.Box 900
NL-1380 DA WEESP
Tel +31-294-477322/477000
Fax +31-294-417772
telex: 14232

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Cantacuzino Institute
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450024 Ufa Bashkortostan
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Fax +7 0107 3472 213196
telex 16297 POTOK

Slovak Republic:

Imuna sp.
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082 22 Sarisske Michal'any
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Fax +42-934 2620
telex 76208 IMMUNA C

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Laboratorioes Leti SA
Parraco Triado 62-68
Barcelona 14

Switzerland:

Swiss Serum & Vaccine Institute
Postfach 2707
CH-3001 Bern
Tel +41-31-980 61 11
Fax +41-31-980 67 75

United Kingdom:

Evans Medical Ltd
Biological Drive
Speke, Liverpool L24
Tel +44-151-486 1866
Fax +44-151-486 5033
telex: 87808 EMHLOR G

Medeva International
Evans House
Regent Park
Kingston Road
Leatherhed Surrey KT22 7PQ
Tel +44-1372-36 41 20
Fax +44-1372-36 41 15

USA:

Connaught Laboratories Inc
P.O.Box 187
Swiftwater, Pennsylvania 18370-0187
Tel +1-717-839 71 87
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Parke-Davis Inc.
870 Parkdale Road
Rochester, MI 48307
Tel +1-810-651 9081
Fax +1-810-656 5508

Wyeth-Ayerst Laboratories Inc
Wasp and Biddle Streets
P.O. Box 304
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13 Annex G: National Pandemic Plan

Please attach here your country's national pandemic response plan.