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INFLUENZA PANDEMIC: PREPARATION IN THE WESTERN HEMISPHERE

Past influenza pandemics have occurred with little warning. In 1918, the lack of an active surveillance system delayed the identification of a pandemic until large increases in disease due to a dramatically different type of influenza virus had already spread widely in different countries. Even with laboratory procedures in place to study influenza viruses, relatively few samples were submitted to the existing World Health Organization (WHO) reference center during the 1968 pandemic. In contrast, today there are four WHO Collaborating Centers for Reference and Research on Influenza, which each year characterize thousands of isolates, identify new viruses using rapid genome sequencing, and communicate results. Moreover, there has been an increased knowledge of animal influenza viruses.

However, prediction of the onset of an influenza pandemic remains impossible, preparation of control measures (such as manufacturing of a new vaccine) takes more time than is available before the pandemic strikes, and keeping stocks of anti-influenza drugs in sufficient amounts is unrealistic. Hence, pandemic planning must be pursued to accomplish two objectives: effective assessment of risk from new viruses; and effective management of risk when the new viruses present with properties to spread widely and cause serious disease.

Technical cooperation provided by the Pan American Health Organization (PAHO) will accelerate the development and implementation of national and subregional pandemic plans emphasizing the areas of overall management, surveillance, vaccination strategies, medical care, medical supplies, and communications. Existing national emergency preparedness committees should activate a multidisciplinary national pandemic planning task force responsible for developing long-term strategies appropriate for their countries in advance of the next pandemic. The responsibility for management of the risk from pandemic influenza rests primarily with national authorities. Therefore, the Subcommittee on Planning and Programming needs to consider the seriousness of a potential influenza pandemic, the options available to confront it, and the recommendations that can be issued to the Member States and the Pan American Sanitary Bureau (PASB) in that regard.

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Introduction

1. During the past century, influenza pandemics have affected different segments of the world population with diverse degrees of impact. During the 1918-1919 Spanish Flu pandemic, subsequently found to be caused by the H1N1 strain, more than 500,000 people in the United States of America and more than 20 million worldwide died of influenza-related complications. Nearly half of those deaths were among persons 20-40 years of age, and case-fatality rates of 30% among pregnant women were reported. The 1957-1958 Asian Flu was associated with an estimated 70,000 deaths and the 1968-1969 Hong Kong Flu was associated with an estimated 34,000 deaths in the United States alone. The clinical attack rate during epidemics range from 10% to 20% in the general population to more than 50% in closed communities, such as nursing homes. Very little is known about the public health significance of influenza in tropical areas, where viral transmission can occur year-round. More than 90% of influenza-related deaths in the United States occurs among persons 65 years of age and older. Hospitalizations are concentrated in population subgroups at extremes of age and in those with underlying chronic respiratory and cardiovascular conditions.

2. The most important strains of human influenza virus are A and B, which are classified on the basis of two surface antigens: hemagglutinin (H) and neuraminidase (N). *Influenza virus A* has several subtypes, of which two, H1N1 and H3N2, are currently of epidemiological significance. The instability of influenza viruses results in constant and usually small changes in their antigenic composition, a phenomenon known as antigenic drift, necessitating corresponding annual changes in the composition of influenza vaccines.

3. The greatest public health concern is the sudden and marked change in *Influenza virus A*, either through mutation or through the exchange of influenza virus genes or the transfer of whole virus among host species into novel, genetically distinct subtypes, in a process known as antigenic shift. The result is the abrupt appearance of a new virus strain to which populations may have no immunity and against which no existing vaccine may confer protection. It is impossible to anticipate when the next major shift, resulting in a pandemic, might occur. In the past, influenza pandemics occurred, on average, three to four times each century, when new viral strains emerged by antigenic shift and were readily transmitted from person to person. Should an influenza pandemic virus appear again, increased volume and speed of international travel, high population densities in many regions, and increased urbanization will increase the likelihood of spread and may put additional severe constraints on the establishment and implementation of timely public health control measures. Although it is not considered feasible to halt the spread of a pandemic influenza virus, the goal should be to limit the burden of disease, minimize social disruption, and reduce economic loss.

4. Recent episodes of animal strains causing disease in humans support experts' views that a new pandemic is inevitable. Epidemiological models project that another pandemic is most likely to result in 57 to 132 million outpatient visits, 1.0 to 2.3 million hospital admissions, and 280,000 to 650,000 deaths in less than two years, in industrialized countries alone.

Epidemiological Situation, Prevention and Control

5. Virological surveillance is the foundation on which national and international influenza surveillance systems are built. Within a country, virological surveillance may consist of a single national laboratory or a national network of laboratories reporting to a central national laboratory that compiles the data and forwards it to WHO. Virological data can be reported by the national laboratory to WHO via the web-based reporting system, FluNet.

6. Influenza activity in the Americas is reported by 16 countries with national reference centers for influenza surveillance: Argentina, Brazil, Canada, Chile, Colombia, Cuba, Ecuador, Jamaica, Mexico, Peru, Trinidad and Tobago, United States of America, Uruguay, and Venezuela. Bolivia and Paraguay began reporting in 2000, but do not have certified national reference centers. Countries with more than one center are: Argentina (3), Brazil (3) and Chile (3). Canada and the United States also have numerous centers. Among the above-mentioned countries, there is a diversity of laboratory working procedures and technical capabilities. However, all institutions perform immunofluorescence and isolation in tissue culture and some perform polymerase chain reaction, hemagglutination inhibition, isolation in eggs, and/or sequencing.

7. The national reference centers have been essential in the development of technical capacity in Latin America, including technology transfer. The Centers for Disease Control and Prevention (CDC) has provided standard reagents.

8. A subset of the isolates is sent to the WHO Influenza Collaborating Center for the Americas at CDC for complete identification and antigenic characterization. Specimens for virus isolation are collected through a sentinel surveillance network of emergency rooms, outpatient clinics, private physicians, or from respiratory disease outbreak investigations. Participating countries in the Influenza Network report morbidity, mortality, epidemiological data, number of cases of pneumonia and other respiratory diseases, number of samples studied, and types of viruses. In fact, most countries have expanded the panel of viruses tested to include adenoviruses, respiratory syncytial virus, and parainfluenza virus.

9. Between 1991 and 1995, the number of strains characterized from Latin America was relatively low. An increase has been observed since 1997, when surveillance and laboratory training organized by PAHO and CDC began and private vaccine manufacturing companies sponsored laboratory work. Further improvements have taken place since the inception of the Southern Cone Network for Emerging Infectious Diseases in 1998. Even though the number of samples and isolates depends on the level of influenza activity each year, it is encouraging to see 1,454 and 1,296 strains isolated in 1999 and 2002 (up to August), respectively. Laboratory experts have observed an increase in the quality of work of national reference centers, which in turn yielded increased viral typing and characterization. A remarkable performance was observed in Argentina, whose network of 62 sentinel physicians, 24 provincial laboratories, and 3 national reference centers produced 550 original positive samples of influenza through the rapid immunofluorescent method and 273 isolates of influenza virus in 2001 (250 A/Panama/2007/99 (H3N2); 1 A/New Caledonia/20/99 (H1N1); 16 B/Johannesburg/5/99; 3 B/Sichuan/379/99; 1 Influenza A (H3N2) and 2 Influenza A without characterization).

10. Unfortunately, the majority of samples obtained are from hospitalized children under 5 years of age. In this population, the rate of influenza virus detected is around 5%. In Latin America the best rate of influenza detection was obtained in the group of adults and children consulting sentinel physicians with an influenza-like syndrome. The detection of influenza virus in this group was 21.4% for type A and 2.5% for type B. This finding has made it possible to obtain strains to be included as candidates for vaccine production for the Southern Hemisphere. Participating countries continue to be urged to increase the number of isolates and shipments to the WHO Influenza Collaborating Center for the Americas at CDC. Ideally, the countries seek to send three shipments corresponding to the beginning, peak, and end of the influenza season. However, there are still logistical and financial obstacles in the transportation of these samples. PAHO has facilitated the customs procedures and provided limited resources for shipping.

11. The enthusiasm of countries to participate in influenza surveillance activities was motivated in part by the national authorities' needs to use local data for making informed vaccination policies' decisions.

12. Most countries in the Americas do not currently include influenza in their immunization policy. Only Argentina (since 1993), Brazil, Canada, Chile, Cuba, Mexico, United States, and Uruguay have yearly influenza vaccination programs for seniors. Furthermore, vaccination policies of Brazil, Canada, Chile, United States, and Uruguay include persons of other age groups at high risk for influenza complications.

13. Data on vaccination coverage for Latin American countries is limited. Brazil's influenza vaccination campaigns target persons 65 years of age and older for 1999-2001, and 60 years of age and older in 2002; 74% to 87% of those population subgroups were vaccinated. An increasing number of doses were administered each year, from 7,519,114 doses in 1999 to 11,026,124 in 2002. Uruguay has provided influenza vaccination for seniors since 1996. The 2002 influenza vaccination campaign in Uruguay succeeded in vaccinating 233,346 people among 815,592 people over 55 years old (29%). Although Uruguay used to vaccinate persons 60 years of age and older, the age group was changed to 55 years and older in 2002. Persons of other age groups with risk factors for influenza complications are offered the vaccine as well. Vaccination coverage in Uruguay has fluctuated between 31% and 41% during 1996-2001. Argentina has an influenza vaccination program for seniors since 1993; approximately 4 million doses of influenza vaccine were purchased in the country in 2002. Chile vaccinates persons 65 years of age and older, health personnel, and people with chronic diseases registered in the public health system. Each year, Chile vaccinates approximately one and a half million people, with coverage above 95% among those aged 65 years old and over.

14. WHO currently has a list of 27 laboratories that produce influenza vaccine, and PAHO purchases from 9 of them (Baxter, SmithKline, Pasteur-Merieux, Chiron Behring and Chiron Biocine, Swiss Serum and Vaccine Institute, Evans Medical, Connaught, and Wyeth). In Latin America, Brazil's Butantan Institute has an agreement with Merieux-Connaught for technology transfer for vaccine production. Currently, Brazil buys vaccines in bulk.

Current Technical Cooperation

15. Influenza surveillance in the Americas is an integral part of the global influenza surveillance that was established by WHO in 1947. The global system provides information on circulating strains of influenza virus and epidemiological trends from 112 national influenza centers in 83 countries, and four WHO Collaborating Centers for Reference and Research on Influenza (Atlanta, London, Melbourne, and Tokyo).

16. The dissemination of surveillance information is facilitated through a web-based network named FluNet. Besides guiding the annual composition of recommended vaccines, the network operates as an early warning system for the emergence of influenza variants and novel strains.

17. Since 1997, PAHO in partnership with WHO and CDC has organized numerous training courses on laboratory surveillance. These activities were made possible through the Southern Cone Network for Emerging Infectious Diseases with the support of PAHO and CDC. This Network has emphasized the implementation of common protocols with

quality assurance systems, technology transfer, and expanded reagent production and distribution.

18. Countries in the Southern Cone have recognized that they are unprepared to control an influenza epidemic of large magnitude; hence, a decision was made to develop comprehensive national and subregional contingency plans for an influenza pandemic with PAHO's technical cooperation. These plans should not only address vaccine availability and population subgroups for priority immunization, but should also include issues involving stockpiling of chemoprophylaxis, clinical training, mass medical coverage, surveillance, prevention, and social communication. In 2002, a workshop, organized by PAHO's Program on Communicable Diseases and the Division of Vaccines and Immunization, was held with the participation of Argentina, Brazil, Chile, and Uruguay, to develop national contingency plans. Thanks to the collaboration of the Malbrán Institute in Argentina, a Spanish version of the WHO Plan for the Global Management and Control of an Influenza Pandemic was made available to use as a framework during this workshop.

19. Before the expected start of the influenza season, the national influenza centers are provided with a kit of laboratory diagnostic reagents which should enable them to determine the type and subtype of influenza viruses circulating during the season. This kit is manufactured for PAHO and WHO by the WHO Influenza Collaborating Center for the Americas located at the CDC in Atlanta, Georgia, and distributed to all centers free of charge.

20. For many years, WHO has held a consultation in mid-February to formulate a recommendation for the composition of inactivated influenza vaccines intended for the following winter in the Northern Hemisphere (November to April). Since epidemics of influenza occur at different times of the year in different parts of the world, the influenza virus is constantly changing, and the use of vaccines is increasing worldwide, the need to review the recommendation twice a year has become evident. Since 1998, a second recommendation is made each September for the vaccines to be used for the following winter in the Southern Hemisphere (May to October) with the participation of a Latin American expert.

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

PAHO and WHO Strategies for Surveillance, Prevention and Control of Influenza

22. Even in the absence of a pandemic, public fear can build rapidly when a few cases of infection in humans with a new virus subtype occur, as was seen in the United States in 1976 and in Hong Kong in late 1997. Such fear about the existence of a dangerous new form of influenza virus creates 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" has been defined that can be applied before the beginning of a pandemic (see Annex).

23. This should assist PAHO and WHO in reporting on novel virus infections of humans and initiate precautionary responses, without creating unnecessary panic. Such an approach 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.

24. The different characteristics of past occurrences show the need for flexible contingency plans capable of responding efficiently to a pandemic threat. A framework prepared by WHO (*Influenza Pandemic Preparedness Plan. The Role of WHO and Guidelines for National and Regional Planning, Geneva, Switzerland, April 1999*) is intended to assist the Organization and its Member States to be prepared to fulfill their roles and responsibilities in this regard.

Programmed Activities

25. In order to be better prepared for the event of an influenza pandemic and reduce morbidity and mortality due to annual influenza epidemics, the following aspects need to be addressed:

- (a) Improvement in the quality and coverage of influenza surveillance. Integrated virologic and disease surveillance is to be supported by the following activities: evaluate national influenza centers and health services systems' capacity to respond; standardize methods and train for laboratory and disease surveillance (develop reagents/manuals, provide training and proficiency testing); facilitate shipment of influenza isolates/specimens; identify gaps and expand geographical coverage; and expand animal influenza surveillance.

PAHO will cooperate with countries in these activities, continue to collect and analyze data on the occurrence of influenza viruses, and provide this information to health authorities.

- (b) Development of national pandemic plans. The national authorities are primarily responsible for the preparation and risk management of a possible pandemic of influenza which should at least include provisions for hospitalizations and treatment of large numbers of people within short periods of time, production and stockpiling of vaccines and antivirals, and risk communication. PAHO strongly recommends that all countries establish, under existing national emergency preparedness committees, a multidisciplinary national pandemic planning task force responsible for developing appropriate strategies to prepare them for the next pandemic. Because of the complexity of the issues described above, the Task Force will benefit from the inclusion of representatives of the national vaccination programs, national reference laboratories, regulatory authorities, health care delivery systems, among others.

PAHO has prepared in collaboration with the Malbran Institute in Argentina a Spanish version of the guidelines for national pandemic plans and will continue to provide technical cooperation for their development in Member States.

- (c) Studies of influenza epidemics to estimate the impact and economic burden of a possible pandemic among high-risk groups and the general population. Some countries have begun studies of the impact of influenza. PAHO will promote and support studies to assess the burden of disease in additional selected countries.
- (d) Assessment of the use of available vaccines and antivirals in the event of a pandemic. PAHO will collaborate with countries.
- (e) Promotion of technology transfer and partnerships for influenza vaccine production in countries of the Region. PAHO should stimulate influenza vaccine production by regional manufacturers following good manufacturers' practices in countries where the national regulatory authorities fulfill WHO recommended functions.
- (f) Improvement of influenza vaccine coverage among high-risk groups during annual epidemics. PAHO has drafted specific recommendations concerning priority groups for influenza vaccination. This draft will be submitted for consideration to PAHO's Technical Advisory Group on Vaccine Preventable Diseases of the Division of Vaccines and Immunization and will guide technical cooperation with countries to establish national policies and set immunization targets.

- (g) Improvement of influenza outbreak control in closed settings. Countries should develop the capacity of rapid response teams to investigate and control influenza outbreaks by considering the use of antivirals and vaccines during annual epidemics in closed settings. PAHO is preparing guidelines for influenza outbreak control.

26. The activities described are essential for pandemic preparedness. PAHO will develop a plan of action based on the WHO Global Agenda on Influenza Surveillance and Control.

Action by the Subcommittee on Planning and Programming

27. The Subcommittee is invited to make observations and issue recommendations on the status of surveillance, laboratory, and vaccine/immunization and on programmed activities related to national and international influenza pandemic preparedness plans.

Annex

ANNEX

Preparedness Levels for Interpandemic, Pandemic, and Postpandemic Periods			
Phase	Characterized by	Explanation	Actions to Be Taken by PAHO/WHO
Phase 0, Preparedness Level 0		No indications of any new virus type have been reported.	Coordinate a program of international surveillance for influenza in humans, with the assistance of four Collaborating Centers.
Phase 0, 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 subtype, 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. Coordinate international efforts to assist national and local authorities reporting the potential pandemic virus in confirming the infection of humans by a novel strain. Heighten activities of the laboratory surveillance network.

Preparedness Levels for Interpandemic, Pandemic, and Postpandemic Periods (cont.)			
Phase	Characterized by	Explanation	Actions to Be Taken by PAHO/WHO
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 subtype, 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.	<p>Announce, with the help of its task force and after international consultation, this Preparedness Level 2.</p> <p>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.</p> <p>Develop a case definition to be used in surveillance for a new virus subtype.</p> <p>Invite a group of countries to participate in determination of the prevalence of antibody to the new virus in the general population.</p> <p>Promote enhanced surveillance activity regionally or internationally.</p> <p>Promote development and evaluation of candidates for production of vaccines against the novel influenza strain.</p> <p>Promote development of reagents necessary to determine the identity and potency of vaccines prepared with the new strain.</p> <p>Promote contingency planning for preclinical and clinical trials of vaccines.</p> <p>Promote the development of strategies for the most efficient use of newly developed vaccines.</p> <p>Recommend that national health authorities take contingency steps that will facilitate activation of their National Pandemic Preparedness Plans.</p>

<p align="center">Preparedness Levels for Interpandemic, Pandemic, and Postpandemic Periods (cont.)</p>			
Phase	Characterized by	Explanation	Actions to Be Taken by PAHO/WHO
<p>Phase 0, Preparedness Level 3</p>	<p>Human transmission confirmed</p>	<p>This Preparedness Level will exist when human transmission of the new virus subtype 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.</p>	<p>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 subtype. 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 coordinated 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 on 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 against the new virus. Encourage international coordination 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.</p>

Preparedness Levels for Interpandemic, Pandemic, and Postpandemic Periods (cont.)			
Phase	Characterized by	Explanation	Actions to Be Taken by PAHO/WHO
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 hemagglutinin subtype 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 into account specific characteristics of the new subtype 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.
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.

Preparedness Levels for Interpandemic, Pandemic, and Postpandemic Periods (cont.)			
Phase	Characterized by	Explanation	Actions to Be Taken by PAHO/WHO
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 antiviral drugs. Seek further support in mobilization of resources for countries with limited capacities.
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.