



# **BRAZIL'S CONTINGENCY PLAN TO CONFRONT AN INFLUENZA PANDEMIC**

**- PRELIMINARY VERSION -**





Health Ministry  
Health Surveillance Secretary

# **BRAZIL CONTINGENCY PLAN TO CONFRONT AN INFLUENZA PANDEMIC – PRELIMINARY VERSION –**

September, 2005

## **NOTE**

This version is under public conference to receive contribution from the Brazilian Contingence Plan preparation to confront an influenza pandemic. Some parts are being elaborated by specific technical groups being concluded on 31/10/2005.

# ABBREVIATIONS

ANF	Nasal Pharynx Inhaled
ANVISA	Sanitary Surveillance National Agency
CCIH	Hospital Infection Control Committee
CGDT	Transmissible Diseases General Coordination
CGLAB	Public Health Laboratories Coordination
CGPNI	Immunization Program General Coordination
CRIE	Special Immuno Biologic Reference Center
CID	Diseases's International Statistics
CONASS	National Health Secretaries Council
COVER	Immuno Preventive and Respiratory Transmissible Diseases Coordination
DAB	Basic Care Department
DAE	Specialized Care Department
DAF	Pharmaceutical Assistance Director's Board
DEVEP	Epidemiological Surveillance Department
DSA	Avian Sanitary Department
EPI	Individual Protection Equipment
ESF	Family Health Strategy
FIOCRUZ	Oswaldo Cruz Foundation
GGTES	Technology for Health Service General Management
IAL	Adolfo Lutz Institute
IBAMA	Brazilian Institute for Environment and Renewable Natural Resources
IEC	Evandro Chagas Institute
IFI	Indirect Immunofluorescence
IgG	Immunoglobulins Antibody Form G Class
IgM	Immunoglobulins Form M class
IOC	Oswaldo Cruz Institute
IPEC	Evandro Chagas Research Institute
IRA	Acute Respiratory Infection
LACEN	Public Health Central Laboratory
LRN	National Reference Laboratory
LRR	National Reference Laboratory (ies)
GGPAF	Harbours, Borders and Airports General Management
GIPEA	Infections and Adverse Events Preventive Investigation Management
GTDER	Emergent and Re-emergent Diseases Technical Management
MPU	Union Public Ministry

NUCOM	Communication Nucleous
RPM	Rotations by Minute
SAS	Health Care Secretary
SCTIE	Secretary of Technology, Science and Strategic Resources
SES	State's Health Secretary
SI-API	Immunization Program Information System
SI-CRIE	Information System for Reference Centers of Special Immune-biologics
SI-EAPV	Post Vaccination Adverse Events Information System
SI-EDI	Immuno Biologic Distribution and Stock Information system
SGB	Guillian Barré Syndrome
SCIH	Hospital Infection Control System
SMS	City Health Secretary
SST	Salt Tampon Solution
SUS	Single Health System
SVS	Health Surveillance Secretary
MDcK	Madin Darby Canine Kidney (Cell lineage for the influenza virus cultivation)
MAPA	Agriculture, Livestock and Provision Ministry
MS	Health Ministry
OMS	World Health Organization
OPAS	Pan-American Health Organization
PAISSV	Evaluation Program Instrument for Supervision of the Vaccination Room's
PBS	Phosphate Tampon Solution
PCIH	Hospital Infection Control Program
PROCC	Scientific Computation Program
PROJU/MS	Justice Attorneyship/ Health Ministry
UBS	Basic Health Unit
USF	Family Health Unit
UTI	Intensive Care Unit
VISA	State's Sanitary Surveillance
VRS	Sincial Respiratory Virus

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# EXECUTIVE RESUME

Influenza pandemics have already caused damages throughout history. Last century at least three big pandemics occurred in which within a few weeks have caused a massive impact on the mortality, affecting mainly children and young adults and causing social rupture situation.

Nowadays there's a concern around the outbreak of a new pandemic block of the virus influenza. It's not possible to predict exactly when the next pandemic will happen neither the extension of the harm and consequences to the world's public health. It is known that this event is unavoidable and may cause serious social and economic consequences. It is estimated that around one quarter of the population might be affected in only a few months. In front of this fact, the World's Health Organization (WHO) is encouraging countries to elaborate or to revise their contingency plans, preparing themselves for the confrontation with a new influenza pandemic outbreak.

The present Contingence Plan approaches the fundamental issues of national pertinence regarding the preparation and the response to a influenza pandemic outbreak. And based on the actual recommendations of the WHO and it has as main objectives to delineate the actions and activities needed to retard the introduction of the pandemic block in the country, minimizing the mortality impact resulting from the dissemination of an influenza pandemic outbreak and its repercussion on the basic health service functioning.

The capacity organization for fast answers to emergency situations such as this, including adoption of proper strategies of information and communication became a priority in public health. The Health Ministry (MS), through Health Surveillance Secretary (SVS) is coordination the process of fast answers through the development of this Contingence Plan along with organs and institutions in and out the Health sector.

According to WHO the strategic actions of a Contingence Plan for an Influenza pandemic outbreak must be at least to understand: the country's infra-structure situation and the activities needed to deal with an epidemiologic emergency situation in different areas (human and animal epidemiological surveillance, health care, prevention and control, civil defense, information and communication, research and legal aspects), defining the responsibilities of each sphere of the government and other government and non-government institutions.

The following issues are essential for the structuration of the country's answer capacity to minimize the impact of an influenza epidemic outbreak: the capacity of previous detection; the use of rational and adequate anti-viral drug and vaccination, considering the real availability and if they are according to the principles and protocols previously established and the development of technological capacity for vaccines national production.

This document was written by members of a technical team especially built for this purpose through SVS/MS based on the accumulated discussions up to this moment of the Brazilian Committee for the Preparation of the Contingency Plan for an Influenza Pandemic Outbreak. (Document # 36, from 22/12/03, published on 23/12/04), the WHO's orientations, the available bibliography over the influenza epidemiologic situation today and the consultation

of the contingency plans from other countries.

It's a preliminary version of the Brazilian Plan, summing up the epidemiological situation today and explaining and adapting the WHO orientations and systematizing the infra-structure situation of our SUS for the confrontation of a pandemic outbreak regarding: epidemiologic surveillance, basic and specialized care, hospital infection control, vaccines and anti-viral use, the current legislation and some technical orientations already existent regarding surveillance, prevention, control of influenza at group and individual levels. The proposed actions and activities are defined according to the different periods and phases of the preparation and express the actual stage of technical discussion over the Brazil's preparation for an influenza pandemic outbreak, still having to incorporate the contribution of other institutional actors and the civil society. The activities proposed must be reviewed constantly according to the evaluation of the epidemiologic situation. It is predicted that the execution will be gradual, according to the concrete risk situation analyses along with the realization of simulations to test the emergency procedures that must be adopted in real situations.

We call the attention for the dimensions of the problem that extrapolate the health sector and there's the need of active participation of the other organs and levels of the government and of the society. This preliminary version must be discussed on the different decision forums of the country's health policies and social control of the Single Health System and in the other decision levels of the federal, state and city government

Considering all Brazil's international commitments regarding the transmissible diseases control, it is expected that this Contingence Plan makes stronger the internal response capacity to the dissemination of respiratory diseases transmission.

## Introduction

The influenza of “flu” is an acute viral infection of the respiratory system, of global distribution and highly transmissible. **(Brazil, 2002)**. The influenza virus are split into A, B and C types according to the typical antigenic profile. Because they are highly transmissible and mutants, the influenza virus, mainly the A type, use to cause outbreaks, epidemics and pandemics, and may cause a high mortality and morbidity.

The pandemic outbreaks of influenza may have serious consequences to the public health and economy. There are no precise world's estimative about the number of cases and deaths related to the influenza. However, pandemics seems to happen every 10 or 20 years (occurred since 1889) and regional epidemics and outbreaks occurs every 2 or 3 years. The biggest pandemic ever happened between 1918 and 1919, the so called “Spanish flu” (due to the death of a Spanish royal family and the big quantity of information given by the communication vehicles of this country). With estimative of the occurrence of more than 25 million death world wide **(Malhotra & Krilov, 2000) (European Community, 2004)**.

An influenza pandemic may be described as an epidemiological event characterized by world wide circulation of a new type of influenza virus to which the population present few or no immunity at all; or of a virus that causes morbidity and mortality that exceed significantly the registered average for a country in outbreaks and seasonal epidemics and that have world-wide spread. Once the influenza outbreaks occurs regularly is extremely important to have the capacity to evaluate is they are able to reach serious epidemic proportions and be converted into pandemics. That way, it's of extreme importance to have an appropriate surveillance system capable of supply precise and opportune warnings.

The pandemics threat with its social, economical and public repercussions force the countries to be alert and to develop contingency plans that point out how to act in emergency situations.

In the last three years Brazil has been developing some activities directed to improve the knowledge about the epidemiological situation related to influenza and the response capacity facing emergency situations. It is detached here the accomplishment of a research of the influenza virus in migratory birds, along with the Brazilian Institute for Environment and Renewable Natural Resources Agriculture, Livestock and Provision Ministry, when it was identified the avian influenza virus of low pathogenicity; the survey, together with Pan-American Health Organization (OPAS) about the seasonality of the influenza virus circulation in a typically tropical region of the country. Ecological surveys about hospitalization due the influenza and its associated causes; the designation of a technical committee to discuss the contingency plan; the development of a scenario survey of a pandemic influenza in Brazil and the organization of an International Seminary to exchange experiences with countries that are advanced in the process of preparing for a pandemic.

### Objectives of the Brazilian Contingence Plan for an Influenza Pandemic

The general objective of the Brazilian Contingence Plan for an Influenza Pandemic is to minimize the dissemination effects of a pandemic block in national territory about the morbidity and

mortality and its repercussion in the economy and in the functioning of the essential services of the countries.

The specific objective of the Brazilian Contingence Plan for an Influenza Pandemic is to:

- Retard the dissemination of a pandemic block among the Brazilian population;
- Reduce the morbidity, mainly of the serious shapes of the disease, and the mortality by influenza;
- Strengthen the infra-structure of the country to deal with epidemiological emergency situations in respiratory transmissible diseases, epidemiological surveillance, laboratorial diagnosis, assistance, vaccination and communication;
- Identify groups of priority to chemical prophylaxis and vaccination, according to different levels of progression of the pandemic and the availability of drugs and vaccines;
- Develop effective mechanisms of technical cooperation and articulation between the surveillances of human and animal influenzas;
- Develop communication and information strategies;
- Develop legal, political-management mechanisms needed to support the process of decision making in epidemiological emergency situations;
- Develop international cooperation mechanisms;
- Develop mechanisms of cooperation with center of scientific and technological knowledge production to study particular aspects of suggested interventions (Effectiveness and efficacy of a new vaccine, resistance to anti-viral, effectiveness of anti-viral use in pandemic situations, adverse events and others);
- Implement mechanisms of intra and inter sector articulation.

The objectives of this Plan will be reached with coordinated efforts of all three government and non-government spheres in its planning and execution. Like any other Plan, this one cannot be static and must be improved according to the operational needs, with the incorporation of new technologies and with changes in the epidemiological scenario.

### **Antecedents of the Contingency Plan for an Influenza Pandemic**

Later 2003, the Health Surveillance Secretary (SVS) of the Health Ministry (MS) constituted a technical committee to prepare the Brazilian Contingence Plan for an Influenza Pandemic, made formal through the document # 36, from 22/12/03, published on 23/12/04.

The committee made 2 meetings (May, 2004 and February, 2005) and adopted as methodology the discussion and elaboration of proposal from 5 groups: Surveillance and Laboratory, Vaccination, Information and Communication, Health Assistance and Infection Control.

Aiming to speed and conclude the Contingence Plan, a work group was formed in August 2005, made by technicians from the Epidemiological Surveillance Department (Immunization, Laboratory and Surveillance), Legal Assistance and communication from SVS/MS; the Specialized Care Department (medium and high complexity) and from the Basic Care Department of the Health Care Secretary (SAS); The Director Board of Animal Defense from The Agriculture,

Livestock and Provision Ministry (MAPA); The General Management Technology for Health Service of Sanitary Surveillance National Agency (ANVISA); The Directors Board of the Pharmaceutical Assistance of the Secretary of Technology, Science and Strategic Resources (SCTIE) to effectively elaborate the referred Contingence Plan.

### **Structure of the Contingency Plan for an Influenza Pandemic**

The structure of the Plan bounces the responsibilities and activities that must be developed for each government and non-government sphere involved. The Plan consists of 8 chapters that include information about:

- Chapter 1: Influenza Epidemiologist, with information about the disease, the structure and the types of influenza virus;
- Chapter 2: Influenza Pandemic and its stages;
- Chapter 3: Brazilian actual structure of Health surveillance;
- Chapter 4: Inter-endemic period – activities developed to assure the contention of an unavoidable pandemic. The coordination of several activities in a pandemic stage such as vaccination, the surveillance, laboratories and health services organization, among others;
- Chapter 5: Pandemic Warning Period – activities that include the preparation of the actual plan, training, division of the responsibilities during a pandemic, simulation exercises to test the plan, communication and other interfaces;
- Chapter 6: Pandemic Period – steps to take when the activities are directed to control the pandemic and minimize its direct effects such as morbidity and mortality, including information about the use of vaccines and anti-viral (prophylaxis and treatment) and its indirect effects such as social rupture. The focus of this chapter is to point out a series of activities that must be developed, sometimes simultaneously coordinated to produce an effective response;
- Chapter 7: After-Pandemic – activities that will be started after the pandemic wave, that also involve the organization of activities of the after event, trying to recover the harm caused. Some examples of activities on this chapter: Restructuration of the health service net, canceling the alternative services created for the pandemic and using others that will be helpful for the maintenance of the health care; the reorganization of activities until a new pandemic stage appears;
- Chapter 8: Organization of three government spheres for the publication, divulgation and application of legislation for compulsory actions related to the contention of the entrance and spread of the pandemic in the country such as: declaration of the pandemic situation, quarantine use priorities, anti-viral and vaccine among others.

## **CHAPTER 1**

### **1.1. Influenza: epidemiological aspects and the risk of a new pandemic**

Influenza, or just flu, is an acute viral infection of the respiratory system with global distribution and highly transmissible **(Brazil, 2002)**. The disease is caused by the influenza virus, a RNA virus. The virus is transmitted in a direct way (mainly through the generation of small drops when the infected person coughs, sneezes or talk but also through the air by the inhalation of small residual particles) or in an indirect way. Influenza has a high attack rate, spreading quickly in closed environments; smaller children of around 2 years old, elderly and individuals of any age with certain chronic or immune-depressive diseases are the group of population of higher risk of complication of the disease, mainly the secondary bacterial diseases. Among the predisposition factors to the acute respiratory infection in children, the nutritional state, the low weight at birth and the number of people by home are expressively determining as well as others such as agglomeration, school level of the family, lack of or inadequate breast-feeding, pollution and passive inhalation of smoke **(NICHOLSON, 1998; COX, 1999; MALHOTRA, 2000)**.

The influenza virus, according to the typical antigenic profiles, are subdivided into 3 types: A, B and C. The A virus causes periodical epidemics and pandemics, with high rates of morbidity and mortality. The B virus is related to sporadic outbreaks and also may cause grave disease.

From the biologic point of view one of the explanations for the emergency of epidemic or pandemic blocks leads to the viral genotype of the virus influenza type A and the existence of multiple reservoir of the infection agent in the nature, what helps the occurrence of specific mutations during the replication process of the viral genotype, promoting the formation of new blocks (also called new variety) in the same subtype. The subtypes are determined by two glycoproteins located in the surface of the viral envelope, the hemagglutinin (H) and the neuraminidase (N). Up to the moment 16 glycoproteins H and 9 glycoproteins N were identified in animals, including mankind.

If this new blocks present some antigenic identity with the previous one, that means they result of a process of evolution inside the same subtype, then they are called drift alterations **(Stamboulia et. al., 2000)**. However, different subtypes infect differently birds and mammals and depending on the conditions of the environment and on the drift alterations, specific subtypes of birds may infect mammals. When this happens, there's a probability of both or more subtypes infect simultaneously the same innkeeper or reservoir. That way, the gene exchange may occur among different subtypes with significant differences in the hemagglutinin and neuraminidase, affecting all the human population susceptible to this kind of subtype **(Malhotra & Krilov, 2000 e Freitas, 2005)**.

Up to 1997, it was believed that it would necessarily have an re-arrangement or an shift alteration in pigs for a bird influenza virus to adapt to the replication in human and cause the disease. That year in Hong Kong for the first time it was documented the direct transmission of the avian influenza virus of high pathogenicity (H5N1) from the bird to humans, meaning that the role of the "gene mixer" so far attributed only to swine may also be developed by humans. Direct transmission episodes avian-human from the block H5N1 has been repeated in some countries of Southeast of Asia since the end of 2003, where the population, for commercial and cultural aspects, have a big interaction with avian and swine. There are evidences of the transmission

inter-human of this block in some familiar clusters, what increases the risk of the emergency of a new pandemic block not only via genetic exchange with block but also through a phenomena known as adaptive mutation that results from the successive passage from an avian block in the human body, through different clusters, acquiring biologic stability enough to a transmission sustained among human beings.

The historical evidences suggest the pandemics occur three to four times every century. Last century three influenza pandemics occurred (“Spanish Influenza” in 1918-19; “Asian Influenza” in 1957-58 and the “Hong Kong Influenza” in 1968-69), and the gap between them was of 11-14 years **(STAMBOULIAN, 2000)**. The worst scenario, the Spanish Influenza, caused from 20 to 40 million deaths worldwide. In all the last three pandemics it was identified an increase of the mortality rate between people with less than 60 years old; in 1918-19 the highest mortality rate was among adults between the age of 20 and 40 years old. **(Canadian Plan, 2004)**.

From the epidemiological point of view the epidemics and pandemics of influenza are related to modifications in the society structure that helps the spread of a new block, in ecological, social and special concrete contexts. That way it must be remembered that the historical context and the stage of scientific knowledge in the last pandemic happened were quite different: The Spanish Flu happened by the end of the World War I, in a moment when the available technologies regarding prevention and infectious diseases control were still too limited (for instance, the synthesis of penicillin and the influenza virus discovery only happened around 10 years after the end of the that pandemic); on the other hand, pandemics of 1957 and 1968 had a much bigger impact on the morbidity than on the mortality.

The evidences created by the analysis of those pandemics and the epidemiological knowledge today allow to cast the following factors that must be considered in the emergency of a new influenza pandemic analysis:

- The appearance of a new block of influenza virus type A, through a process of genetic exchange between different block species or adaptive mutation;
- The efficiency of the transmission of the new infectious agent;
- The pathogenicity and the virus power of the new block;
- The existence of big population contingents with few or no immunity to this new block;
- The rates of effective contact, meaning the probability of an infected subject effectively transmit the disease to another susceptible subject;
- The technical-scientific basis of the society and the democratic access to advances;
- The fast response capacity of the public health authorities.

In today’s scenario there’s a big risk of the emergency of a new influenza pandemic that may have an important impact in the mortality, the public security and in economy of affected countries. It is estimated that a pandemic virus coming from Asia could get to Americas in less than 3 months, with fast potential of spreading throughout this continent.

## **1.2. Estimative on the Impact of an Influenza Pandemic in Brazil**

### **Ongoing Research – Scenarios an Influenza Pandemic in Brazil**



## **CHAPTER 2**

### **Influenza Pandemic and its stages**

The World Health Organization (WHO) defines an influenza pandemic in different periods and stages, that approaches the human and animal influenza a risk for the public health. This common terminology will make easier the articulation, the standardization and the transparency of the communication and of the efforts to plan the response facing an influenza pandemic in Brazil and in different countries.

The WHO defines the following periods and stages to be observed in the planning of the responses to an influenza pandemic (**frame 1**):

**Frame 1. Periods and Stages of an Influenza pandemic, according to WHO**

Period	Stages	WHO's definition	Recommendations
<b>Interpandemic</b>	<b>Stage 1<sup>1</sup></b>	There's no detection of new subtypes of influenza virus in humans. Presence of a viral subtype that already have caused human infections in the past in animal reservoirs and low human infection risk.	Strengthen the preparative for a influenza pandemic in world scale, regional and national.
	<b>Stage 2<sup>1</sup></b>	Transmission risk increase to humans with a new virus subtype that circulate between animals referred in Stage 1.	Reduce to minimal the risk of transmission in humans, detect and notify quickly the transmission when it occurs.
<b>Pandemic Warning</b>	<b>Stage 3<sup>2</sup></b>	Detection of one or more cases of human infection with a new virus subtype, without inter-human transmission or, if existent, limited to intimate contacts (rare cases).	Fast characterization of the viral subtype and detection, notification and opportune response to additional cases.
	<b>Stage 4<sup>2</sup></b>	Conglomerate detection of inter-human transmission with few cases of geographically located, what indicates that the virus didn't acquire good adaptability to human beings.	To stop the new virus in the focuses or to retard its spreading aiming to win time to speed the preparation measures such as vaccine preparation containing the pandemic block.
	<b>Stage 5<sup>2</sup></b>	Detection of the inter-human transmission conglomerates still geographically limited, however reaching a biggest number of people, indicating that the virus is adapting itself better in human beings (considerable pandemic risk).	Contain or retard the spreading to avoid a pandemic an win time to speed the anti-pandemic response measures.
	<b>Stage 6</b>	Pandemic: transmission amplified and sustained in the population in general.	Reduce the repercussion of the pandemic.
<b>After-Pandemic</b>	<b>Stage 7</b>	Returns to the Inter-pandemic Stage.	Inter-pandemic Period.

As it can be observed, this division is based on the risk evaluation of the disease spreading in different situations. That way, continents and countries worldwide will be able to find different

<sup>1</sup> The difference between **Stages 1 and 2** is based on the infection risk or sickness in humans coming from blocks that circulates among animals. For this evaluation it was considered the factors: pathogenicity of the block in animals and humans; infection presence in domestic animals or in silvester fauna, if it's an enzootic or an epizootic virus, if it's located geographically, among other criteria)

<sup>2</sup> The difference between **Stages 3, 4 and 5** is based on the evaluation of the pandemic risk. For so it is considered the factors: transmission rates, geographical location and spreading, genes coming form human block presence, among others.

pandemics, expecting to change between them all the time, either going forward or returning back in the risk scale, depending on the effectiveness of the actions of control and surveillance adopted at each moment.

Taking the WHO as reference, the literature related to previous pandemics, the Contingence Plans of Canada, US and England and the analysis of the epidemiological situation worldwide today, it is proposed the adoption of internal warning level for Brazil (**Frame 2**). Detaching that the premise to define such levels is the appearance of a new block of pandemic and its adaptation to human beings will happen in the Asian continent e afterwards spread to other continents. From the moment that the efficiency of the transmission of a new pandemic block is confirmed the time of entrance of it in our country varies from a few days to three months, mainly because of the velocity of the transportation and the globalization process. It's worth to remind that the warning levels must be considered flexible and mutable according to the pandemic scenario today.

Below are, for planning and response, the warning levels in Brazil.

**Frame 2. Brazil's warning levels, according to different Pandemic Periods and Stages**

Periods	Stages	Periods	Stages
<b>Inter-pandemic</b>	<b>Stage 1<sup>3</sup></b>	There's no detection of new influenza virus subtypes in humans in Brazil and worldwide	Keep the routine activities of surveillance, prevention and control of influenza.
	<b>Stage 2<sup>3</sup></b>	There's no detection of new influenza virus subtypes in humans in Brazil. Presence of a virus subtype that already caused infection in humans in the past in reservoir for animals and low risk of human infection.	Initiate the process of preparing or revising the Contingence Plan; Adapt the strategies of surveillance of the animal influenza. Strengthen and improve the epidemiological surveillance nationally.
<b>Pandemic Warning</b>	<b>Stage 3<sup>4</sup></b>	Detection of one or more cases of human infection with a new virus subtype in some foreign country of other continent.	Speed the process of preparation and revision of the Plan; Keep the surveillance system in alert for the detection, notifications and proper investigations of grave forms of respiratory diseases coming from the affected region.
	<b>Stage 4<sup>4</sup></b>	Detection of conglomerates o inter-human transmission with few cases from other continent.	Conclude the Plan elaboration; keep the surveillance system in alert for a detection, notification and investigation of grave forms of respiratory disease coming form other affected region in strategic areas (big urban centers, harbors, international airports); Plan and execute the simulation emergency actions.
	<b>Stage 5<sup>4</sup></b>	Detection of conglomerates o inter-human transmission with a bigger number o cases in other continents and/or pandemic block detection in some south America country (except Brazil).	Launch level of warning in the country: detection and investigation of grave forms of respiratory diseases in people (big urban centers, harbors, international airports and other points of immigration).
	<b>Stage 6<sup>4</sup></b>	Detection of pandemic block in Brazil.	Launch maximal warning level: detection, notification and investigation of suspect cases in national territory; adopt measures of transmission blockage of primary and secondary cases; evaluate need of activity suspension of collective character.
<b>Pandemic</b>	<b>Stage 7</b>	Epidemic in Brazil due dissemination of pandemic block.	Minimize morbidity, mortality and the economical and social impact.
<b>After-Pandemic</b>	<b>Stage 8</b>	Pandemic Block of influenza virus stops circulating and returns to endemic levels.	Conclude analysis of the impact on morbidity/mortality, economical and social. Reorganize the structure of assistance net; Return to Stage 1.

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Chapter 4, 5, 6 and 7 present the specific action and activities for each level of pandemic warning in Brazil.

<sup>3</sup> The difference between **Stages 1 and 2** is based on infection sickness risk in human coming from animal blocks. For this evaluating consider the following factors: pathogenicity of the animal and human blocks, infection presence in domestic animals, if it's an enzootic or an epizootic virus, if it's located geographically, among other criteria)

<sup>4</sup> The difference between the **Stages 3, 4 and 5** is based on the pandemic risk. To evaluate such risk some factors are considered, according to the current scientific knowledge: transmission rate, geographic location and spreading, disease gravity, genes originally from human blocks (when the virus comes from animal's blocks) and other scientific criteria. The difference between **Stages 5 and 6** is based on the evaluation of introduction risk and eminent spreading of the pandemic block in the country.

### **CHAPTER 3**

#### **Actual Structure of Surveillance, Health Care and Information and Communication in Health in Brazil**

##### **3.1. The Influenza Surveillance in Brazil**

The Health Ministry began in 2000 the implementation of an Influenza Surveillance nationwide which objectives are to monitor the influenza virus blocks that circulate in Brazilian regions, respond to unusual situations, and evaluate the vaccination impact on the disease, to allow the morbidity and mortality tendencies associated to the disease and to disseminate epidemiological information.

A surveillance sentinel strategy based on a net of health units (basic care, and ERs) and laboratories. Considering as a requirement to the implementation of a sentinel unit the previous existence of an infra-structure and management organization of the unit, localization next to the reference laboratory, the attendance of spontaneous demand on individuals from different ages, the existence of a state's or city's reference laboratory with capacity to make the diagnosis of the respiratory virus and also the interest of surveillance team and laboratory's and local managers compliance.

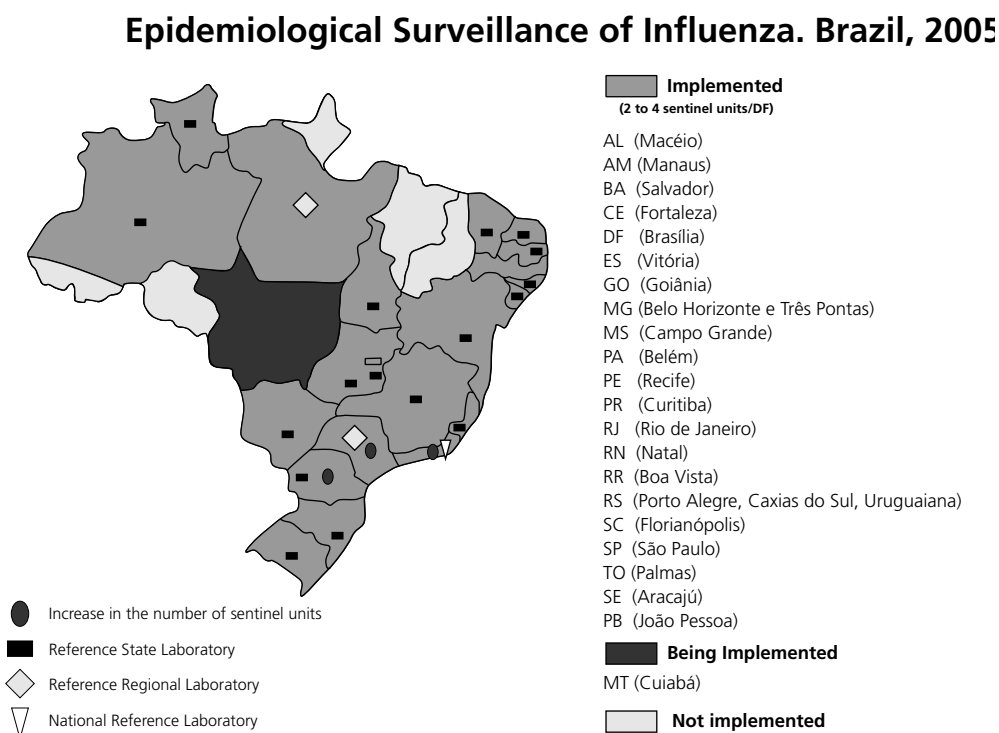
The sentinel units has as responsibility to collect and send to the reference laboratory clinic specimen of an intentional sample from patients that look for attendance in order to process, analyze and inform on a weekly basis the cases proportion of flu syndrome related to the total of the clinic cases attended in the unit, spread by age. The flu syndrome definition adopted in Brazil is: individual with acute respiratory disease (with maximum duration of 5 days), presenting fever (still referred), cough and sore throat, in the absence of other diagnostic. If the sentinel unit's information organization allows instead of the previous definition, it can be straight computed the following diagnosis of acute respiratory infection in the superior treatment: J00, J02.9, J03.9, J04.0, J04.1, J04.2, J06, J10, J11.

The information system of influenza surveillance, called SIVEP\_GRIPE, has an online structure, allowing to make data and information available simultaneously for all surveillance net.

The influenza Surveillance system also foresees the detection, notification and investigation and outbreaks control, independent of the sentinel net, in consonance with the actual rules about notification of transmissible diseases in the country. It also foresees the routine analysis of ecological data about hospitalization and deaths caused by influenza and the associated causes, what allows the observation of a pattern in the flu occurrence in regions with distinctive climatic aspects.

Today, the Influenza Observation System involves 46 sentinel units, most of them located in the main cities of 21 states of the 5 Brazilian regions (Figure 1), 18 state laboratories, and two national reference laboratories. It foresees up to the end of the year of 2006 that this system will be working at least in all Brazilian capitals.

**Figure 1. Influenza's Epidemiological Surveillance, Brasil, 2000 a 2005**



### 3.1.1. Laboratories Net of Influenza Virus in Brazil

The monitoring of influenza is an activity of world scale and today it mobilizes a net of 110 laboratories in 80 countries coordinated by world reference centers linked to WHO: Institute of Medical Research of United Kingdom (England); Diseases Control Center (CDC), Atlanta (USA); CSL Limited in Victoria (Australia) and National Institute of Infectious Diseases, in Tokyo (Japan).

In Brazil there are registered in the WHO as Center of Reference for Influenza as follows: Evandro Chagas Institute (IEC/SVS/MS), Adolfo Lutz Institute (IAL/SP) and Institute Oswaldo Cruz (FIOCRUZ/MS). In the country's internal laboratories net organization, the two first are classified as Regional Reference and the last one as National Reference.

With the implementation of the Surveillance System for influenza in the country, the laboratory net was being gradually amplified, according to the system expansion itself. It was then created on a state's level the laboratories net, responding to the Regional and National Reference Centers (**Frame 3**)

**Table 3. Relation of coverage of Reference Laboratories for Influenza Surveillance (situation in 25.08.2005)**

Reference Laboratory	States Referred
Oswaldo Cruz Foundation	BA, ES, MG, PR, RJ, RS*, SC
Adolfo Lutz Institute	DF, GO, MS, SP e TO
Evandro Chagas Institute	AL, AM, CE, PA, PB, PE, RN, RR e SE

Expansion Stage (\*).

The influenza virus presents an antigenic diversity every year. Therefore, laboratorial analysis are of great importance to monitor the type of block circulating in our country, making possible to better analyze the vaccine block indication and possible detection of pandemic blocks. The virus detection success depends mainly on the clinic sample conditions, meaning the collect, storage and transport.

The indirect immune fluorescence test is made in a state's level, through a commercial kit composed by a panel of monoclonal antibodies that allows the detection of influenza virus type A and B, respiratory sicial, adenovirus and parainfluenza of types 1, 2 and 3. This test is fast and may allow to obtain the result few hours after the collect of the clinic material.

The virus detection by isolation of cell cultures or embrionary eggs constitutes the standard gold method for detection of influenza's virus. The method recommended for identifying the subtypes of influenza is the inhibition of the hemagglutination test (HI) that allows to classify according to antigenic variations present in each viral sample. For this analysis an antigenic panel and specific serum are used for each variant, supply by WHO. The detection by viral isolation and HI is made by three reference laboratories and representative samples of the identified virus belonging to each subtype are sent to DCD/Atlanta to confirm and analyze with an amplified panel of antigen and immune serum.

The molecular method utilization amplified the knowledge field of the influenza's virus and is being used to follow the mutations of this virus nature. The sequence of the nucleotide of the influenza's virus genes, mainly the H gene, followed by a phylogenetic analysis allows the genetic variations ministration that may occur annually, gather the similar blocks, identify mutant blocks and help in the virus comprehension. Such techniques are being used by reference laboratories and allow a better comparison of circulating blocks of virus with the vaccine's blocks.

The serum tests for anti-influenza antibody's detection may be done to evaluate the immune response after vaccine and in retrospectives serum-epidemiological surveys. There's no serology indication for acute cases diagnostic.

### **3.1.2. Epidemiological Situation of Influenza in Brazil.**

In the period of 2000 and 2005 the attendance proportion of influenza syndrome in the sentinel unites varied between 5 to 255 by epidemiological week, reflex of new units incorporation in the Surveillance System, particular aspects of the services organization in each of this sentinel units and real modifications ion the seasonal epidemiological profile of influenza A, Sincicial Respiratory Virus, Adenovirus, Parainfluenza 1 and influenza B. among this detected types of influenza virus the majority was of A/H3N2 and influenza B, similar to the international standard circulating. The complete antigenic characterization of these blocks made clear that all viral subtypes were direct or indirect part of the vaccines composition used in south Hemisphere.

In the period of 2005 and 2005 influenza's outbreaks were detected in closed communities (Indians village, companies, prisons, asylum and school) in some federal units and 5 community outbreaks, the majority happening in cities of the extreme southeast of Santa Catarina. In the closed communities outbreaks investigated, the average rate of influenza syndrome outbreak

was of 22,4%, varying from 3,5% in avian abatement units with sick young adults to 48% in an asylum. In this spots the residents had an average age of 81 years old (gap of 46 to 97 years) and the health professionals with 38,5 years old (gap of 19 to 68 years). In community outbreaks it was identified an average of 25% of the attendance for influenza syndrome in the cities affected (varying from 21 to 29,6%). The aiming influenza's blocks identified in these outbreaks were Influenza B/Hong Kong; A/Tocantins (H3N2); A/Fujian (H3N2); A/Korea (H3N2) and Yamanshi and /Jiangsu.

### **3.1.3. The Surveillance facing Influenza's Pandemic in Brazil.**

In general lines, the strategic role to be played by surveillance in the distinct periods and stages proposed by WHO goes from continuing improvement of the quality of Influenza 's Surveillance System in the interpandemic period, passing by the monitoring and analysis of the epidemiological scenarios, including the unusual situation; by the detection and investigation of precocious cases for the control measures direction and by the evaluation together with the other involved areas of the effectiveness of the implemented measures.

That way, according to each level of warning corresponding recommendations explained on Frame 2, the following strategic actions or activities may be cast:

#### **Stage 1:**

- Follow, evaluate and improve the Influenza's surveillance system ;
- Monitor the epidemiological actuation;
- Evaluate the effectiveness of the annual vaccination with the epidemic blocks;
- Detect, investigate and control of influenza's outbreaks in which may occur grave forms of the disease;
- Produce and disseminate epidemiological information;

#### **Stage 2**

- Improve the technical articulation with the organs in charge of the viral influenza's surveillance;
- Improve the follow-up of the epidemiological situation of influenza national and internationally;
- Produce and disseminate epidemiologic information;

#### **Stage 3**

- Develop mechanisms to notify and investigate grave severe cases of respiratory diseases in individuals proceeding from affected areas, improving the technical articulation among harbors, airports and boarders, the hospital surveillance and the CCIH (including the pneumonias' surveillance).

- Promote epidemiological surveys to develop pandemic scenarios;
- Develop adequacy proposals of the Influenza's Surveillance to confront outbreaks of pandemic blocks: design special systems of information and services organization and develop/update emergency capacitation modules for professionals of the surveillance net;
- Produce and disseminate epidemiological information;

#### **Stage 4**

- Improve the mechanisms of precocious detection of severe cases of respiratory diseases in individuals coming from affected areas, mainly from big urban centers;
- Evaluate the action of Stage 3, identify red flags and correct them;
- Structure and capacitate an specialized team for fast dislocation and proper investigation of the cases;
- Promote the development of proposal for the actions' effectiveness evaluation protocols (individual/collective) as well as the use of specific technologies;
- Conclude the analysis of pandemic scenarios;
- Produce and disseminate epidemiological information;

#### **Stage 5**

##### **a) Detection of cases in countries that don't have borders with Brazil**

- Update the pandemic scenario and adequate the Plan if necessary;
- Develop activities of active surveillance for precocious detection of server cases of respiratory diseases in individuals proceeding from affected areas, mainly from big urban centers and others spots of entrance of foreign in the country;
- Coordinate the emergency capacity of VR in the country, giving priority to the strategic areas (borders area and big population agglomerates);
- Produce and disseminate epidemiological information;

##### **b) If any case is detected in a boarder country;**

- Activate Civil Defense
- Develop active surveillance activities to detect precocious severe cases of respiratory diseases if any point of the national territory, mainly in big urban centers and others spots of entrance of foreigners in the country;
- Execute, along with ANVISA, a special system of surveillance for harbors, airports and borders.
- Produce and disseminate epidemiological information;



### **Stage 6**

- Direct the activities of transmission blockage;
- Activate civil Defense;
- Based on situation analysis, direct and follow-up the other measures of prevention and control;
- Produce and disseminate epidemiological information;

### **Stage 7**

- Operate simplified system of surveillance;
- Monitor the situation and redirect the actions, if necessary;
- Detect the appearance of new pandemic wave;
- Monitor, along with DAF/SCTIES and ANVISA, the use of antimicrobials and antivirus regarding resistance and adverse reactions, aiming to give directions the adequate clinical handling and treatment;
- Produce and disseminate epidemiological information;

### **Stage 8**

- Readjust the system of Influenza's epidemiological surveillance system to the new scenario;
- Evaluate the impact of the pandemic in the morbidity and mortality;
- Produce and disseminate epidemiological information;

The chapters 4, 5, 6 and 7 present actions and activities specific for each pandemic warning in Brazil.

## **3.2. Assistance Net – The acting of the Basic Health Care**

The basic care consists on a group of action, of individual or collective character situated on the first level of the health care systems, aiming to promote health, aggravation prevention, treatment and rehabilitation. These actions are not limited to those procedures included in the Basic Assistance Group table from SIA/SUS, when the Floor of Basic Care was implemented. The amplification of this concept becomes necessary to advance towards a health system centralized in life quality of people and their environment.

The Basic Care Organization, based on the law number 8080, has as fundament the Single Health System (SUS) principles: definition of Health as a fundamental right, being responsibility of the state to provide the necessary conditions that assure the equal universal access to services and actions to promote, protect and recover the individual and collective's health.

Today, the basic care in Brazil involves two models: a traditional, in which the health units are composed by a general doctor, pediatrician, gynecologist, nurses and nurse assistants, without

the presence of a community health agent; the other model, denominated Family Health Strategy, is composed by a multi professional team (doctor, nurse, nurse assistant and other 4 community agents) that have access to resources that may be used to precocious identification of risk areas and suspect cases of infectious diseases and aggravations in their coverage area. The population coverage of the ESF is limited to big urban centers. Today there are 23.097 registered working teams, with 200.193 community agents given coverage to a population of 74.523.803 habitants (what corresponds to around 42% of the Brazilian population), and 33.623 nurse assistant, 31.301 nurses and 31.403 doctors **(See Frame 4 and 5)**.

It's important to bounce that in pandemic situations, both models will have to work as one, with all professionals working in an organized way according to a pre-established protocol.

**Quadro 4. Número de profissionais envolvidos na Estratégia de Saúde da Família e da Atenção Básica, Brasil.**

Professional Kind	No. of Professional ESF	No. of Professional Basic Care
Community Health Agent	219.019	Does not have
Nurse Assistant	33.623	327.297
Nurse	39.576	65.920
General Doctor	31.403	80.384
Fisiatristician	Does not have	750
Fisio therapist	Does not have	18.655
Pneumologist	Does not have	3.707
Infectologist	Does not have	2.938

**Frame 5. Number of establishment of Basic Care, Brazil, month and Year**

Kind of establishment	Number establishment
Health Post	11.398
Health Center or Basic Unit	25.429
Mixed Unit	778
General Hospital	1.406

### **3.2.1. Activities developed by professionals in the Family Health Team**

Community Health Agent: this professional is the link between the population and the health team and some of the responsibilities are:

- Make the mapping and the registration of all families of the area, that must be done on a regular basis, during the family visit;
- Identify the individual and family members at risk situation as well as risk area and identification of partners and resources in the area that might be empowered by the team;
- Orient the population regarding the correct use of the health service and developed actions of educations and surveillance emphasizing the promotion and the prevention of diseases;
- 

Nurse Assistant:

- Uses nursing procedures among the technical and legal attributions in the different environments such as Family Health Units (USF) and at home, according to the planned by the team;
- Searches for active cases under surveillance and education actions in health for risk groups;
- Prepares the patient for the medical and nurse consult;

Nurse:

- Makes the nurse consult and direct cares in emergencies and urgencies;
- Plans, manages, coordinates, executes, evaluates the USF as well as make the supervision and coordination of the capacitation actions of community agents and nurse assistants aiming to develop their functions;
- Execute actions of integral assistance at all stages of life with actions of epidemiological and sanitary surveillance. Also executing health actions in different environments;

Doctor:

- Clinic consult to the user and execution of procedures in the health units as well as at home if necessary, executing integral assistance actions in all life cycles;
- Make the ready attendance in urgencies and emergencies, directing to services of biggest complexity when necessary and assuring the continuity of the treatment at the USF;
- Check and certificate deaths;

### **3.2.2. Team acting for basic care confronting Influenza's pandemic**

- Knowledge of the areas and the reality of the families for whom they are responsible for, identifying most common problems to which population is exposed;
- Elaboration along with the community of plans to confront the health problems and factors that put at stake the health, following the National Plan directives;
- Execute according to the qualification of each professional the procedures of health surveillance and epidemiological surveillance;
- Give integral assistance to the population, responding to the demand in a continuous and rational way;
- Promote intersectorial actions with formal and informal organizations existing in the community to confront the identified problems;

- Participate intensively of the elaboration and execution of vaccine campaigns, making professionals capable and keeping they informed regarding diseases, vaccine doses, vaccine schema, counter-indication, among others;
- Act in the dissemination of information, guiding the public about the risks of the contagion and ways to avoid it;
- Evaluation of the Basic Health Care Units (UBS) and USF, risk of transmission and the need of isolation in suspect cases, making an active search for contact aiming to guide and manage the contacts prophylactic measures;
- Articulation with other areas of public health such as epidemiological and sanitary surveillance keeping the team always informed about what is the actual situation;
- Identification of risks spots in the area such as schools, childcare centers, asylums and others.

### 3.3. Assistance Net – Specialized Care in Brazil

#### 3.3.1. Hospital Net structure

Today the health assistance net in Brazil has 466.863 beds, being 381.050 of them designated for SUS (81% of the total). As for the classification of the referred beds of SUS, 104.888 (27,5%) are for surgery patients, 255.038 (67%) are for clinic patients and 21.124 (5.5%) are complementary beds that include 1.852 beds for intensive care for children, 3.003 beds for neonatal beds, 8.248 beds for intensive care for adults and also 4.696 beds for intermediate units and 3.325 isolation beds. This last ones represent 40,3% of the isolation beds in the country (Frame 6).

Given the characteristics of the actual Brazilian hospital nets, a concentration of health care establishments are noticed and thus of beds in the area of more technology concentration, notoriously in the southeast region. Specifically in this region we have 82,7% of the total SUS existing beds (154.939), being 50,20% (6.578) of the beds for intensive care in Brazil and 37,95% (1.262) of SUS isolation beds.

**Frame 5 – SUS beds existing by region – Brazil 2005**

Regions	Bed Numbers														
	Total Clinics	SUS Clinics	Total Surgeons	SUS Surgeons	Total ICU Neonatal	Neonatal ICU SUS	Total Adults ICU	SUS Adults ICU	Total Pediatric ICU	SUS Pediatric ICA	Total UCI*	UCI* SUS	Total Isolation	SUS Isolation	
North	18846	15706	8646	6391	130	100	443	311	114	95	260	217	360	323	_
Northeast	86331	76352	40161	32342	706	438	2422	1423	416	317	1416	1164	966	874	_
Centre West	24569	18863	13079	9289	398	224	989	594	312	232	312	246	286	226	SUS
South	52771	40662	22946	15667	787	620	2497	1788	477	383	783	624	728	640	381050
Southeast	107095	103455	61452	41199	2583	1621	6535	4132	2067	825	3301	2445	1679	1262	Total
Total	289612	255038	146284	104888	4604	3003	12886	8248	3386	1852	6072	4696	4019	3325	466863

\*Intermediate Care Units

As for the adequacy of the beds to respond to a pandemic situation, there's no information on the data available bank of the Health Ministry regarding this issue. **Frame 7** shows the services pointed out by the respective managers as being the reference center for attending patients with suspect/diagnostic of acute respiratory syndrome (SARS). However, there's no objective information regarding the infra-structure today installed in these establishments.

A public consultation is being done about the policy for critical patient care, which predicts the regulamentation of the intermediate care units in general. Long-term speaking, the implementation of this new policy foresees the restructuration of the units that provide critical patients care in general through the increasing of the available beds and its adquation regarding physical infra-structure and equipments.

**Table 2 – Hospitals pointed out by theirs managers as Reference centers for the attendance of suspect/confirmed cases of Acute Respiratory Syndrome.**

State	HOSPITAL
AC	General Clinic Hospital Rio Branco
AL	School Hospital Hólvio Auto
AM	FMT-Hospital of Tropical Medicine
AP	Transmissible Diseases Center of Specialities Hospital
BA	Octávio Mangabeira Hospital
CE	Hospital of Infeccious Diseases São José
DF	HRAN (Regional Hospital Asa Norte)
ES	University Hospital Cassiano Antônio de Moraes/IESP
GO	Hospital Anuar Auad (Tropical Diseases Hospital SES-GO)
MA	Tarquínio Lopes Filho Hospital
MG	Hospital Emergency Room of Venda Nova
MG	Association of Research Assistance of Uberlândia
MS	Santa Casa de Campo Grande
MT	Hospital ER Municipal de Cuiabá
PA	University Hospital João de Barros Barreto
PB	University Hospital Lauro Wanderley (Cidade Universitária)
PE	University Hospital Universitário Oswaldo Cruz
PI	Instituto de Doenças Tropicais Natan Portela
PR	Hospital Ministro Costa Cavalcanti
	Hospital Universitário Regional do Norte do PR
	Clinics Hospital – UFPR
RJ	University Hospital Clementino F. Filho – UFRJ
	State's Institute of Infectology
RN	Hospital Giselda Trigueiro
RO	Hospital Cemetrón
RR	Hospital Rubens de Souza Bento
RS	Hospital Nossa Senhora da Conceição (Rua Francisco Frein)

SC	Hospital Nereu Ramos
SE	Hospital João Alves Filho
SP	Hospital Servidor Público Estadual
	Hospital São Paulo/Universidade Federal of São Paulo
	Instituto de Infectologia Emilio Ribas
	Hospital de Clínicas da UNICAMP
TO	Community Hospital Comunitário of Palmas

AS for the National Policy for Urgencies Care – conducted by Documents GM nº 2.048/03, nº 1.863/03, nº 1.864/03 nº 2.072/03 – specially the Mobile Attendance of Urgency Services, there are 94 services implemented or being implemented, with 727 teams for basic life support and 190 teams for advanced life support. At this stage 598 townships are already being attended with a coverage of 82.188.798 habitants. A concentration of services in the southeast region is observed which detains 42,5% 9310) of the teams installed for basic support and 43% (82) if the advanced support **(Frame 8)**. It is important to remind that the SAMU implementation supposes the effective regulation of the references and counter-references in the attendance of emergencies and not only transportation of patients to the units that provide urgencies assistance to the population.

**Table 3 – Mobile Attendance Service – implemented and being implemented – by region**

Region	Basic Support Unit	Advanced Support Unit	Nº of townships attended	Population
Center West	89	25	128	8.019.437
Northeast	195	49	167	19.574.520
North	67	16	49	5.8000.819
Southwest	310	82	134	38.699.206
South	66	18	120	10.094.816
Total	727	190	598	82.188.798

Source: General Coordination of Urgency and Emergency /DAE/SAS 19/08/05

As for the actions to be triggered in a pandemic, the technical protocols must direct the health care lines providing the directives for the rational organization of the health assistance net. That way several competences must be defined regarding the interventions needed amongst the different levels of care: Basic Care, Medium and High Complexity.

It is the local manager's responsibility to make viable the applicability of the protocols previously defined, diagnose the needs of investment in local health as well as assure the attendance flow with reference and counter-reference plans for the users affected. That way the participation and sensibilization of the managers instances (town and state), predicting the sharing with the National Council of Townships Secretaries of Health and with the National Council of State's Secretaries of Health, must be bounce to boost the executive component of the Contingence Plan for Influenza's Pandemic in Brazil.

Regarding the financing in the emergencial situation the resources source must be defined as well as the way the resources will be passed to the third parts. The investments with capital expenses must be made under the Contract Celebration model and with Health Ministry convention which is the better way to assure the follow-up of the investments made. As for the current expenses it may be possible to re-pass Fund to Fund (Strategic Actions Fund and Compensations – FAEC - for instance).

It's important to bounce that any action of Health care must be based on the principles that guide the Single Health System (SUS) notoriously the Decentralization of Management, because the government sphere disposes of specific responsibilities.

### **3.3.2. The Infection Organization and Control at Health Services.**

The National Health Agency (ANVISA), through the Infections and Adverse Events Preventive Investigation Management (GIPEA) coordinates the Hospital Infection Control Program (PCIH) which activities are delineated by the Law number Leinº 9431 from January 6th, 1997. This law disposes about the obligation of the hospitals to maintain the Hospital Infection Control Program and create a Hospital Infection Control Committee (CCIH)

The directives and norms that make viable the planning of the Program were defined by the document GM nº 2616, from May 12th, 1998. According to this document the Hospital Infection Control Committee must be composed of consultatnt and executive members, these last ones being representants of the Hospital Infection Control System (SCIH) and responsible for the operationalization of the programmed actions of the Hospital Infections Control.

At township and state's levels the Hospital Infection Control Committee are responsible for coordinating the activities of controlling and preventing, connected to the national directives.

At the Health Services, the CCIH coordinate the epidemiological surveillance actions, supervising technical-operational norms and routines related to the prevention and control of infections, capaciting employees institutional professional, develop actions for the rational use of antimicrobians, germinicides and medical-hospital material and investigate epidemiology of cases and outbreaks, implementing immediate measures of control, among other activities.

A recente survey from the Public Health University of São Paulo, along with ANVISA, was developed aiming to evaluate the organization of the hospitals infections control, in which state's and town's health managers and brazilian hospital mangers had to answer a questionnaire. In the 26 states and Federal District the CCHIs are formed and working inserted in different organs: Sanitary Surveillance, epidemiological surveillance and Health Care, except the state of Amapá, Acre, Roraima e Santa Catarina. From the 1009 (17,9%) townships that answered the questionnaire, all of them assure the adoption of infections control actions by the township township health management, since the publication of the document 2616/98.

As for the health services, the incorporation of preventive and controlling actions of the hospitals infections occurred in an homogenic way between the hospitals in the study and the most present actions were the nomination of CCIH (76% of hospitals) and the monitoring of the hospitals infections (77%). More complex actions were less present in the answers, for instance,

the development of infections control programs (49%), specific trainings about infections control (44%) and adoption of outbreaks contention measures (33%). Only 8% of the hospital researched indicated the use of diagnostic criteria for hospital infections of the NNIS/CDC (Horan TC, 2004), officially adopted by Brazil since 1995 and validated in several countries. The majority of the hospitals in the country have no microbiology laboratories: 46,29% in Northeast, 45,45% in North, 41,64% Center West, 26,28% in South and 24,62% in Southeast.

It was possible to notice with this survey that the health system couldn't incorporate actions of preventions and control of the hospitalizations in a homogenic way, following the model of the Committees and of a specific program for this end. A big number of hospital do not have a structured CCIH, working and capable of acting in the investigation and prevention of hospital diseases.

ANVISA considers that actions must be developed aiming to assure the quality of the health care regarding the investigation and control of hospital infections: review the actual model of prevention of hospital infections with the partnership of state's and township managers in the decentralization of the infection control actions; guide the adequacy of the infection monitoring related to the health care, com standardized indicatives and adjusted to the local need; encourage the restructuration of the microbiology laboratories in the country, emphasizing the standardization microorganisms identification techniques and the determination of its sensitiveness; direct the policies of financing to health care, linked to the adoption of control and prevention of risks measures in health care.

### **3.4. The acquisition, commercialization, distribution and use of vaccine and antiviral against influenza in Brazil.**

#### **3.4.1. A vaccine against Influenza**

The continuous impact caused by the infection by the influenza's virus, not only in individuals but also in the populatio in general, is motivating the development of new vaccines. Among them is detached the development of attenuated virus vaccines, innative vaccines that have adjuvants and vaccines produced in cell cultures instead of embrionary eggs of chickens. It is important to consider the vaccination strategies that assure the access to main target groups (more susceptible), based on WHO recommendation.

In Brazil today the inactive vaccines against influenzaare used, and they differ regarding the components of the viral particle in the vaccine (Murphy, 1996). These components split into three types (Kibourne, 1994):

- Whole virus vaccine, composed of the viral whole particle, including lipids of the innkeeper cell membrane. It presents a high immunogenicity and it's more reative; it's not indicated for children under 12 years old, due frequen fever reaction;
- Fractionated vaccine of "split", is fragmentated by the exposition to detergents an purified ina way that stop the antigenic form the virus surface and some viral nucleoprotein
- Sub unitarian vaccine that contains only the protein from the haemagglutin and neuraminidase surface .



In a general way, the sub Unitarian and the “split” type vaccines induce the serologic response in a similar way and they are less reactive and their use is approved for children under the age of 8. In Brazil the vaccine against influenza used is the inactive, fractionated and purified types.

The vaccination scheme with the inactivated differs regarding the number of doses and volume to be administered, using as base the immunogenicity and reactogenicity of the vaccine according to the age. In children under the age of 8, the immune response is inferior when compared to adults. That way it is recommended the immunization scheme with two doses for children at this age, with an interval of at least one month between the doses (Farhat, 2000) (Table 1).

**Table 1- Administration Scheme of the vaccine against influenza**

Age	Dose (ml)	Number of Doses
6 – 35 months	0,25	1 – 2 *
3 – 8	0,50	1 – 2 *
≥ 9 years old and adults	0,50	1

Source: CGPNI/DEVEP/SVS (modified from Farhat, 2000)

(\*) It must be added two doses with an interval of 4 to 6 weeks in children under the age of 8 when they receive the vaccine for the first time.

The inactive vaccine against influenza is recommended, since 1940, as the main mean to prevent influenza and its main complications such as secondary bacterial pneumonia, primary viral pneumonia, the exacerbation of basic chronic diseases (pneumopathy and cardiopathy, nephric diseases, hypertension, diabetes and immunodeficiency) and death (Fong, 2003).

The antigenic changes of the influenza virus circulating required annual alteration in the vaccine composition according to the standard viral circulation detected through the Global Influenza Surveillance System, coordinate by WHO that defines annually the composition for the vaccines for the south and north hemispheres. After this process the vaccine enters in the industrial production process. Today the virus for inactive vaccines are produced in embryonic eggs of chickens and from 4 to 6 months are needed to produce the doses at sufficient number for the world demand. There are, however, genetic recombination techniques of the influenza virus for the vaccine production that allow the shortness of that period.

### 3.4.1.2. Vaccines indication against influenza in Brazil

Brazil has a public policy using strategies of national campaign for vaccination of 60 years old individuals and more since 2000 and in 1999 the population that received the vaccine was established for the aged of 65 or more. Since its implementation the vaccine coverages in the campaign overcame the target of 70% all years and are increasing the percentage of vaccine coverage in all Brazilian townships from 88,43% to 95,42%. In the year of 2005 the vaccination campaign reached the coverage of 84% of the 10,6 million individuals with more than 60 years old.

The vaccine is available in the Immunization Reference Centers (CRIE) for other groups considered of bigger risk for the complications of the disease because of a pathology of basis: cardiopathy, nephropathy, diabetes mellitus insuline-dependent, hepatica cirrhosis haemoglobinopathy, DPOC bearer, immunocompromised or HIV bearers, transplantation patients and families that are in contact with patients previously mentioned. The vaccine is also available for Indian population, prisoners and professionals that work in prisons and health professional.

According to Barros, Daufenbach, Vicente & cols., "there are still conclusive surveys over the impact of the vaccination strategy against influenza in Brazil. Preliminary data from a survey made to evaluate the efficiency of the vaccination (Brondi e cols., 2001), using as indicator the charge of morbidity by causes attributed to influenza (influenza, pneumonia and bronchitis, appointing some differences between the Brazilian regions: comparing the number of hospitalization by causes attributed to the influenza in population over 65 between the years of 1998 and 2000, it was observed the reduction of 15,4% of the hospitalizations in south region and an increase of 6,8% in north region. The regression analysis use for monthly data of hospitalization for six years indicates heterogeneous tendencies that may be related to the seasonal differences in the virus circulation between the regions that present remarkable climate differentiation. In south and southeast regions the seasons are well defined and with a temperate climate, while north region (where the Amazonian basin is located) the climate is tropical, hot and humid during all year. The results of this survey have been demanding a deeper discussion over the need and viability of the adaptation of the vaccination against influenza strategy today practiced in the country because of the seasonal variations pointed above (EPIDEMIOLOGICAL newsletter – year 04 - Nº 01 - 02/02/2004)

### **3.4.1.3. Vaccine against influenza Production**

The biggest vaccine production capacity is in Australia, Canada, France, Germany, Japan, Europe and United States (together they used to produce and distribute 262 million vaccine doses in 2003, corresponding to 95% of the vaccines against influenza in the world (DAVID, 2005).

In Brazil, as a strategy to assure self-sufficiency in production of immunobiologicals, a National Program of Self-Sufficiency in Immunobiologics in 1998 (PASNI) was created by the Health Ministry, with investments of around USD150 million in the modernization of the installations and equipments of public laboratories that produce serum and vaccines. Financial resources for the amplification of the capacity of national vaccine against influenza production are being invested since 1999, emphasizing the logistics and the transfer of technology to the BUTANTAN Institute (SP). BRL 34 million were invested by the MS for the acquisition of equipments and around BRL20 million by the state of São Paulo for the construction of the production plant. All this effort aims the national self-sufficiency by 2008.

Butantan Institute is including the clinic rehearsal of the vaccine with aluminium hydroxide that allows to prepare vaccines with ¼ or less of the antigen dose, increasing, therefore, the capacity of production with the same physical plant. The results in animals are ready and the clinic data will be ready in September 2005. Brazil will be the pioneer in the use of this technique, that was recommended by other researches.

### **3.5.1.6. Development of pandemic vaccine in Brazil**

For vaccine production some seed breed distribution mechanisms were established through international centers of reference established by WHO. The adequate breeds for seeds have to have a adequate antigenic structure, good development in culture and absence of contamination danger for the staff manipulating it. On the other hand the big number o chicken embryo needed to constitute a difficult practice. Some measures are also being studied to accelerate the procedures of authorization of production of a vaccine against a pandemic block.

The epidemiological surveillance needs to be detached because is the basis for the determination of the composition of the vaccine against influenza and which antiviral agents must be considered as auxiliars to the vaccine use (De Jong et al ., 2000).

#### **The continuity of this topic is ongoing**

### **3.5.1.7. The Immunization Program Structure in Brazil**

The National Program for immunizations (PNI) is linked to the Epidemiological Vigilance Department and Health Ministry (DEVEP/SVS/MS) and aims to contribute with the prevention and control of immune predictable diseases of epidemiologic relevance in the country.

The PNI counts with 25 thousand public posts of vaccination in the entire country and in annual campaigns this number gets to 130 thousand posts and 38 Centers of Reference for Special Immunobiologic (CRIEs), in the 27 federal units. 245 million doses of immunobiologic products are distributed every year. The Program's action uses resources for the supply of resources (vaccines, serum and other immunobiologic products) for the sufficiency on the production of vaccines for the amplification of the cold's net.

The storage of the used immunobiologics by the PNI in the 27 federal units is done by a cold net in shish resources are being invested of equipments aiming to provide a more effective logistics in the vaccine's distribution from big urban centers to regions of difficult access (Attachment 7).

To promote a better information quality of the management of immunobiologics in the country, the PNI counts with the following information systems: SI-CRIE, SI-API, SI-EDI e SI-EAPV. Their objectives are:

- SI-CRIE: registers the applied doses of the vaccines, including the one against influenza. It contains data of identification, indication motive, diseas e's basis, applied doses and adverse events registered;
- SI-API: registers the applied doses of the vaccines, including the one against influenza in the vaccination rooms of the net in a daily bulletin by health establishment, in the ages of under 1 year, 1 and 2 years, 3 and 8 years, 9 and 12 years, 13 and 19 years, 20 and 59 years, 60 and over.
- SI-EDI: controls the movimentation of immunobiologics all over the country, informing the vaccines quantities acquired and distributed to the townships and also presents the consolidated by type of physical loss (example: expiring date, temperature alteration)

- SI-EAPV: consolidates the notifications of adverse events after the vaccination time-related to the vaccines administration. It is implemented in the state's health secretaries that are responsible for the entrance of the data in all townships;

### **3.5.2. Use of Antiviral for the prophylaxis and Treatment Influenza**

For most viral diseases there's no specific treatment. However, in the influenza's case, available medicines already exist, with efficiency not only for the treatment but also for the prophylaxis of the disease which use acquire a strategic role in the initial phases of the influenza's pandemic, presenting evidences that do not interfere in the inactive vaccines against influenza.

There are two types of antiviral medicines available today that have their role in the prevention and treatment of the influenza's infection:

- Amantadine and Rimantadine, that act as inhibitors of the ions M<sub>2</sub> channels; interfere in the reproductive cycle of influenza but are not effective against influenza B.
- Zanamivir and Oseltamivir, that act inhibiting the replication of the influenza virus A and B, classified as neuraminidase inhibitors;
- The Amantadine and Rimantadine have 70-90% of efficiency in the prevention of the influenza infection. As therapeutic, when administrated in 2 days from the beginning of the disease they are able of reducing the duration of the disease non-complicated due to the A influenza infection in about one day but they still are not able to reduce the disease gravity. Both induce the resistant viral block's emergency, particularly the Amantadine when used for cases treatment.

The zanamivir and oseltamivir when administrated in two days are able to reduce the less grave diseases' duration of influenza A and B in about 1 day. Data suggest the development of the influenza resistance during the treatment is lower when with the use of neuraminidase inhibitors than with ions M<sub>2</sub> channels inhibitors. Studies have shown that both inhibitors of neuraminidase are similar in efficiency against influenza in laboratories. (Attachment 8).

#### **3.5.2.1. Antiviral Availability in Brazil**

From the antiviral recommended for the prophylaxis and treatment of influenza, three are available in Brazil. They are:

##### **Amantadine:**

- Registered as antiparksonian, recommended for prophylaxis
- Commercial Name: Mantidan
- Presentation: 100 mg tabs

**Rimantadina:**

- Not registered in Brazil;
- Recommended for prophylaxis and treatment;
- Presentation: 120 ml bottle (50 mg/5ml)
- Commercial Name: Flumadine (Estados Unidos)
- Presentation: : Forest tabs

**Oseltamivir:**

- Registered as antiviral, recommended for prophylaxis and treatment;
- Commercial Name: Tamiflu
- Laboratory : Roche
- Presentation: 75mg tabs

**Zanamivir:**

- Registered as antiviral, recommended for treatment
- Commercial Name: Relenza Diskhaler
- Laboratory : Glaxo Wellcome S.A
- Presentation: inhaling powder

The neuraminidase inhibitors have a higher cost than the M2 channels inhibitors.

The supply security is an issue that needs to be discussed once the existent supply of antiviral is limited worldwide and is also primarily distributed by the private sector. It is expected that the global supply of antiviral is quickly consumed in the beginning of a pandemic. It still needs to be discussed the priorities of the supply and distribution as well as the diversity of available antiviral for public health use, given the expected supply will be lower than the demand.

**3.5.2.2. Planning for distribution and use of Antiviral**

A well succeeded intervention with antiviral will demand:

- A safe supply;
- A well planned distribution and a monitoring system under the responsibility of federal, state and township spheres;
- Ability to reach priority groups;

- Fast diagnostic test availability;
- Increase of the virus surveillance, the virus resistance to antiviral and the adverse effects associated to the medicine;
- Clinical orientation for the proper use of the antiviral;
- Protocols of study to increase the efficiency of antiviral in the treatment and prophylaxis of a pandemic;
- Efficient communication and educative materials about antiviral for workers of the public health in general.

## **CHAPTER 4**

### **Interpandemic Period**

In this chapter, we have made priority the routine activities related to influenza prevention, surveillance and control, and the undertaking of some essential activities for the preparation of a pandemic outbreak of influenza, particularly referring to the planning of the infrastructure needed for the following periods. This planning includes the projection of needed number of beds, including Intensive Care Unit (ICU) and isolation beds, for the different pandemic periods; the list of reference services for initial stages; the forecast of alternative services that may be used; the estimation of quantity and cost of individual protective equipment (IPE) and materials for the cleaning, disinfection and sterilization of articles and environments, among others.

The activities will be distributed by stages and described in components, such as surveillance, laboratory, basic and hospital assistance network, vaccines and antiviral drugs use, and communication.

#### **Stage 1**

The recommendations for this level are to keep the routine activities of influenza surveillance, prevention and control.

#### **Human Surveillance**

- To keep the routine influenza surveillance and to extend it with the purpose of giving it a greater national cover;
- To periodically assess influenza surveillance in Brazil, seeking to enhance surveillance in municipalities and states which do not function adequately;
- To investigate outbreaks in closed communities and/or with notification of severe cases, jointly with municipality and state health offices;
- To enhance the technical interface with animal influenza surveillance, for the notification of birds death in a location where an outbreak of influenza is occurring in humans, as well as for the notification of these outbreaks in locations where hogs and birds are raised;
- To collaborate with influenza investigations in migratory birds, jointly with MAPA and IBAMA;
- To enhance data analyses of hospitalization and mortality rates for influenza and chargeable causes;
- To assess the impact of vaccination against influenza in partnership with the general coordination of the National Immunization Program;
- To further studies on the seasonality of influenza virus circulation in distinct Brazilian regions;
- To assess effectiveness of use of antiviral drugs in situations of closed community outbreaks;
- To extend the publicizing of epidemic information on influenza, and associated morbidity and mortality by means of the Ministry of Health's website, class associations; epidemiologic papers and reports, scientific events, among others;
- To monitor the world epidemiologic situation;
- To contribute for influenza world surveillance.

#### **Laboratory**

- Consulting/supervision, in States, of national labs that integrate the influenza epidemiologic surveillance system.

- Training for the technicians who diagnose Influenza in the States.
- Support to training of sample collection carried out by LACEN for the health professionals of the sentinel units who present problems in the quality of collected samples.
- Decentralization of the cell culture for the State of Rio Grande do Sul (RS).
- Implementation of the Influenza diagnose (IFI) in the lab on border city of Uruguaiana/RS.
- To assure (to make available the acquisition of raw-material, kits and equipment) maintenance of laboratory diagnose activities for influenza in the States.

## **Animal Surveillance**

**In development. To be concluded on 10/31/2005**

### **Basic Care**

- Knowledge of the field and of reality of the registered families, identifying most common problems to which that population is exposed and the main risk groups.
- To undertake, according to each professional's qualification, the basic procedures of epidemiologic and sanitary surveillance, according to the epidemiologic reality of its area (case notification and investigation, blocking transmission of infectious diseases by means of vaccines and/or chemical prophylactic agents etc.).
- Mapping schools, nursing homes, and other concerned units in their areas of action.
- Periodic technical training/update in relation to epidemiologic situation, handling and surveillance of acute respiratory infections.
- To participate in annual campaigns for influenza vaccination.
- To estimate need for clinical treatment of community pneumonias.
- To implement assessment process of Basic Care and its adequacy to the epidemiologic profile in local levels.
- To promote intersectoral actions and partnerships with formal and informal organizations existent in the community for facing together identified problems.

## **Assistance Network – Hospital Care**

**In development. To be concluded on 10/31/2005**

### **Assistance Network – Hospital Infection Control**

- To train/update health professionals on infections control norms in health services, IPE, disinfection and sterilization of medical articles and environment cleaning (**Attachment 4**).
- To organize a national reserve of individual protective equipment (IPE) and diagnose methods for a quick distribution in health services, if necessary.
- To assess influenza morbidity and mortality rates (current strains) for estimating additional needs in services (number of beds, IPE, alternative services etc.) and of health professionals during a pandemic.
- To identify establishments that meet requirements of organization, infrastructure and isolation which will compose the reference services network for serving patients suspect of being infected with the new strain of influenza (**Attachment 10**).

### **Immunization**

- To study affordability of introducing a flexibility in the vaccination against influenza in the northern region of the country, based on available evidence;
- To implement strategies, in partnership with STD/AIDS programs, Health in Prison System/ DAPE/SAS, DESAI/FUNASA, Scientific Societies and Commission for Mobilization, in order to extend the vaccination covering for individuals pertaining to already defined risk groups;



- To develop strategies for obtaining estimations on the quantity of special populations to be vaccinated;
- To implement publicizing of indications for existent special immunobiological agents and the address of the CRIE together with Class Associations; Class Councils and Non-Governmental Organizations (NGOs), using informative materials like handbills, folders, signs, primers etc.;
- To hold meetings for discussing adverse events post-vaccination with national producer laboratory representatives, ANVISA, scientific societies, MPU;
- To investigate and follow adverse events temporarily associated to the vaccine against influenza;
- To find the current quantity of human resources involved in the vaccination actions;
- To recommend and vaccinate with trivalent vaccine the professionals under greatest risk of exposition to influenza (Health Professionals);
- To strengthen training or update actions for human resources in information system of the National Immunization Program, vaccination room and cold chain in Brazilian states;
- To invest financial resources by means of the Ministry of Health for building up the facility and acquiring equipment for producing vaccine in the Butantan institute (foreseen to be concluded in March 2006);
- To assure supply of embryos (eggs) for the production of vaccines, by means of contacts with producers associations and to elaborate, jointly with other related bodies, the technical norms for national production of microorganisms-free eggs (in process);
- To assure at least 6 to 8 microorganisms-free embryos suppliers (progressive need up to 220,000 eggs a day for 25 days, within 5 years);
- To participate in already scheduled international meetings (September and October 2005) for discussing the production of vaccine against pandemic influenza;
- To invest in the building and/or making adequate the Cold Chain in the Brazilian territory, and in the acquisition of equipment for facilitating a more resolving logistics of vaccine safe distribution in the country;
- To define flow of vaccine distribution of producer Butantan Institute for states and municipalities, optimizing vaccine time of arrival in locations of use and storage capacities;
- To find the current capacity of vaccine storage in cold chambers in states and the need of adequacy of the Cold Chain Centers;
- To find with State Coordinators of Immunizations the installed capacity and need of thermal preservatives, ice and thermometers for end-use, evaluating the responsibility of acquisition;
- To value costs and benefits of the use of thermal tape (3M) or digital thermometer in thermal boxes for monitoring temperature in vaccines transportation.

#### **4. Data record and information generation**

- To carry out the data record and information generation using SI-PNI;
- To make available SICRIE information for assessment of the population vaccinated against influenza, in the vaccination rooms, identifying reason for indication, base diagnosis, age group and gender;
- To make available data of applied doses against influenza in the campaign actions and in special situations, by vaccination room, municipality, region and state;
- To implement distinguished record of vaccine doses against influenza in CRIES, constantly updated by health technicians and information system users;
- To strengthen use of the daily standardized bulletin of applied doses against influenza for record in the API.

**Clinical handling and use of antiviral/antimicrobial agents**  
**In development. To be concluded on 10/31/2005**

**Communication**

Action: mobilization for case surveillance

Sensitization of people who travel to Eastern regions from where there is suspicion of origin of the pandemic strain

- bird farmers
- importers/exporters
- sports players
- Airlines and Maritime Companies

**Stage 2**

It is recommended, in this level, to begin the preparation or revision process of the Contingency Plan; to make adequate surveillance strategies of animal influenza; to strengthen and improve epidemiologic surveillance of influenza in national scale.

**Human influenza surveillance**

- To keep, evaluate and enhance actions of Stage 1;
- To extend the publicizing of epidemiologic information of influenza, associated morbidity and mortality rates by means of the Ministry of Health's website, class associations; epidemiologic papers and reports, scientific events, among others;
- To evaluate, jointly with environmental bodies and MAPA, the risk of dissemination through migratory birds;
- To begin the preparation or revision process of the Contingency Plan.

**Laboratory**

- To keep, evaluate and enhance actions of Stage 1.
- To create and keep interchange with other international laboratory centers for Influenza, specially the ones existent in the Americas.
- Analysis of the laboratories situation of States: CE, MG, MS and AM, aiming to implement Cell Culture technique in these places.
- To identify which LACEN could carry out molecular biology techniques, with the purpose of helping works of the Reference Laboratories.
- To enhance and assure conditions for carrying out molecular biology techniques in reference laboratories.
- To hold meetings among human and animal Influenza laboratories (for the latter, MAPA) for discussing and defining joint actions of laboratory diagnosis of the Influenza virus.

**Animal influenza surveillance**

**In development. To be concluded on 10/31/2005**

**Assistance Network – Basic Care**

- To keep, evaluate and enhance actions of Stage 1.

**Assistance Network – Hospital Care**

**In development. To be concluded on 10/31/2005**

### **Assistance Network – Hospital Infection Control**

- To keep, evaluate and enhance actions of Stage 1.

### **Immunization**

- To keep, evaluate and enhance actions of Stage 1;
- To extend vaccination cover in risk groups;
- To provide technical support for states in the preparation of national plans of readiness for pandemic, including guidelines on the existent logistics and need of emergency operation for carrying out strategies and estimation of demand for vaccines in various pandemic scenarios;
- To give continuity and assure training and/or update of health professionals involved in immunization actions;
- To optimize the process of allantoic liquid collection and purification process of the embryo in order to be able to produce two vaccine doses by egg;
- To carry out Handling Course of Solar Energy Powered Cooling Equipment for Medium Level (40 hours);
- To carry out supervision on Cold Chain in states: PI, PE, MA, AP, ES, GO, RN and SP.

### **Clinical handling and use of antiviral/antimicrobial agents**

**In development. To be concluded on 10/31/2005**

### **Communication**

Action:

- warning in airports, seaports and borders;
- publicizing of precautionary measures that travelers should take and how to act in case of symptoms;
- intensification of stage 1 actions.

## **CHAPTER 5**

### **Pandemic Warning Period**

In this chapter, we have made priority the activities that should be developed in pandemic warning period, which consists of actions and activities essential in the preparation of the current plan, training, division of responsibilities during a pandemic, simulation exercises for testing the plan, communication and other interfaces.

It is necessary to structure reference hospitals for prior detection, treatment and isolation measures, in addition to training health professionals who act on the basic network relating to reference flow and prior establishment of infection control and isolation measures. Infection control measures in health services should be publicized in advance in order to prevent transmission within hospital environment to other patients or to health professionals. The health professionals should be trained in advance about diagnosis and adequate treatment and for using correctly individual protective equipment (IPE), disinfection and sterilization of hospital articles and environment cleaning (**Attachment 4**).

### **Stage 3**

It is recommended in this level to accelerate the preparation or revision process of the Plan; to keep the surveillance system alert for opportune detection, notification and investigation of severe forms of respiratory disease in people coming from the affected region.

#### **Human influenza surveillance**

- To intensify actions of Stage 2;
- To publicize, in partnership with MAPA and ANVISA, warning to travelers who are heading to or returning from affected areas;
- To accelerate the preparation or revision process of the Plan;
- To keep the surveillance system alert for opportune detection, notification and investigation of severe forms of respiratory disease in people coming from the affected region;
- To implement the process of following and evaluating influenza surveillance in Brazil, including the resistance situation of epidemic strains to antiviral agents in use in the country;
- To improve data analysis of hospitalization and mortality rates for influenza and chargeable causes.

#### **Laboratory**

- To elaborate protocols for identifying the new strain in Brazil.
- To improve training in IAL of technicians in states: CE, MG, MS and AM in the technique of cell culture.
- To find the biosafety situation in the LACEN.
- To program training for the LACENs, with laboratories level 2 and 3, thus enabling them to detect the pandemic strain.
- To evaluate, jointly with ANVISA, the moving of efforts to make feasible in reasonable time the introduction of laboratory reactive agents and raw materials donated by the WHO or other countries for antigenic characterization of detected strains in Brazil.
- Articulation with Cell Culture Laboratory/IAL so that they provide cells (MDCK) to laboratories with capacity for using cell culture technique in the Influenza surveillance network, in the pandemic period.
- To create interchange of technical information among laboratories of human and animal Influenza (for the latter, MAPA), specially in South America and countries bordering on Brazil.

- To assure the supply of kits for quick diagnosis to Seaports and Airports which receive international travelers.
- To elaborate biosafety manual for manipulation and transportation of the pandemic strain and to make it available for all the Influenza surveillance network in Brazil.

### **Animal influenza surveillance**

***In development. To be concluded on 10/31/2005***

### **Assistance Network – Basic Care**

- To keep and enhance actions of the previous stage.

### **Assistance Network – Hospital Care**

***In development. To be concluded on 10/31/2005***

### **Assistance Network – Hospital Infection Control**

- To keep and enhance actions of the previous stage.

### **Immunization**

- To keep and enhance actions of the previous stage;
- To develop technology for the production of vaccines for the circulating viruses, assuring line of production of seed virus and potency reactive agents of trivalent vaccine;
- To produce vaccines against influenza in the Butantan Institute (proposal of reaching self-sufficiency until 2008);
- To evaluate jointly with ANVISA the necessity of clinical studies for registration of the nationally-produced vaccine (proof of equivalence and effectiveness) when the product is on stages 2 and 3;
- To register the vaccine in Brazil through request in ANVISA;
- To register the vaccine against influenza produced by the Butantan Institute in WHO;
- To evaluate if the flow of direct distribution by the Butantan Institute to South and Southeast Regions would optimize the distribution time;
- To reach hard-access areas with solar energy powered coolers;
- To establish strategies and storage norms for hard-access areas.

### **Clinical handling and use of antiviral/antimicrobial agents**

***In development. To be concluded on 10/31/2005***

### **Communication**

- To keep, evaluate and enhance actions of the previous stage.

## **Stage 4**

It is recommended in this level the conclusion of elaboration or revision of the Plan according to the epidemiologic world scenario; to keep the surveillance system alert for opportune detection, notification and investigation of severe forms of respiratory disease in people coming from affected region in strategic areas (great cities, international seaports and airports, among others); to plan and carry out simulation of emergency actions foreseen in the Plan.

### **Human influenza surveillance**

- To keep and enhance actions of the previous stage;
- To obtain and publicize as much clinical and epidemiologic information as possible on the cases and their contacts in the affected region;

- To conclude the elaboration or revision of the Plan according to the epidemiologic world scenario;
- To keep the surveillance system alert for opportune detection, notification and investigation of severe forms of respiratory disease in people coming from affected region in strategic areas (great cities, international seaports and airports, among others);
- To plan and carry out simulation of emergency actions foreseen in the Plan;
- To elaborate or improve protocol for investigation of suspect cases in travelers;
- To elaborate proposal and material for emergency training for epidemiologic surveillance teams.

### **Laboratory**

- To keep and enhance actions of the previous stage.
- To speed up the supply of kits and raw materials to laboratories.
- To assure the supply of embryos for viral replication in reference laboratories.
- Situation analysis of border laboratories in order to possibly implement laboratory and epidemiologic surveillance of Influenza in the locations: Oiapoque/AP, Tabatinga/AM, Foz do Iguaçu/PR, Guajará-Mirim/RO e Pacaraima/RR.
- To elaborate and provide training of new laboratory technicians for Influenza diagnosis (IFI).

### **Animal influenza surveillance**

***In development. To be concluded on 10/31/2005***

### **Assistance Network – Basic Care**

- To keep, evaluate and enhance actions of the previous stage.

### **Assistance Network – Hospital Care**

***In development. To be concluded on 10/31/2005***

### **Assistance Network – Hospital Infection Control**

- To keep, evaluate and enhance actions of the previous stage;
- To update infection control measures if necessary;
- To assess capacity of assistance (number of beds, isolation etc.) and to define alternative strategies for patients isolation and treatment.

### **Immunization**

- To keep, evaluate and enhance activities of the previous stage;
- To evaluate and discuss the need for eventual expansion of physical area of production plant (incubation area), capacity of around 25-30 million doses, after the optimization of the productive process with optimum yield. In order to respond to the need of doses in a pandemic, it should be evaluated the identification of circulating virus and yield in the productive process;
- To assure financial reserve funds for undertaking quick effectiveness and safety studies of a new pandemic vaccine on target-groups;
- To define groups beforehand for vaccination with monovalent pandemic vaccine.

### **Clinical handling and use of antiviral/antimicrobial agents**

***In development. To be concluded on 10/31/2005***

**Information, Communication and Social Mobilization**  
**In development. To be concluded on 10/31/2005**

**Stage 5**

In this stage, considered as intermediary between the dissemination of a pandemic strain at world level (including border countries) and its detection in the country, it is recommended to set maximum alert level in the country for prior detection, notification and investigation of suspect cases coming from affected areas, in strategic points of the national territory.

**Human influenza surveillance**

- To activate foreseen mechanisms in the CIEVS;
- To raise sensitiveness of the epidemiologic surveillance system;
- To set up and carry out specific training for group of specialists who will help in the investigation of suspect cases in any point of the national territory (includes respiratory transmission diseases surveillance technicians, technicians who have concluded training and who are currently training in EpiSus, pulmonologists and infectologists);
- To implement, jointly with ANVISA, an emergency plan of surveillance in seaports, airports and borders;
- To intensify mechanisms of production and dissemination of epidemiologic information.

**Laboratory**

- To identify municipal laboratories, laboratories from Federal, State and private universities that may be integrated as collaborators in the Influenza surveillance network, carrying out the IFI technique.
- To elaborate orientations to laboratory professionals on the correct and necessary use of IPE during the pandemic.
- To assure the supply of IPE for all laboratory professionals who are analyzing pandemic strain samples.
- To train a few LACENs in techniques of molecular biology, so that those help reference laboratories during pandemic.
- To train municipal and university laboratories which are able to carryout the Influenza diagnosis (IFI).
- To assure speeding up the delivery of raw materials to LACENs and reference laboratories.
- To intensify interchange with WHO and other international laboratories for obtaining a series of pandemic strains.

**Animal influenza surveillance**

**In development. To be concluded on 10/31/2005**

**Immunization**

- To keep, evaluate and enhance actions of the previous stage, with emphasis on production and/or acquisition of vaccines against pandemic strain;
- To gather with CGPNI technicians to create indicators that favor the evaluation of vaccination strategies during pandemic, so that adjustments can be assured if necessary, comprising distribution, storage and services.

**Infection Control**

- To keep, evaluate and enhance measures of the previous stage.
- To assess the capacity of health services on the number of beds and isolations.

- To train health professionals and managers for detecting new cases and controlling infection within health services.
- To verify the carrying out of infection control procedures to prevent intra-hospital transmission.

### **Basic Care**

- To keep, evaluate and enhance actions of the previous stage.
- To act on the spread of information, guiding the public on the risks of transmission and the ways to avoid it.

### **Hospital Care**

**In development. To be concluded on 10/31/2005**

### **Immunization**

- To intensify the preparation process for vaccination, when the vaccine against pandemic strain is available: to prepare record bulletins of doses for outbreak or epidemic situations for the vaccine against influenza and to establish ways of information flow; to hold meetings with DATASUS staff for discussing and making adequate the SI-PNI for data record and flow of information on vaccination against influenza for other age groups; to carry out training for the SIPNI Support Group, State Coordinators of Immunizations and Supervisors; to define instrument for data collection that enables analysis during pandemic (SI-PNI), to assure reliability of PNI information system data.

### **Seaports, airports and borders surveillance.**

**In development. To be concluded on 10/31/2005**

## **Stage 6**

This stage contemplates exclusively the detection of pandemic strain in Brazilian territory. It is recommended in this level to set maximum alert level in the country for prior detection, notification and investigation of suspect cases in any point of the national territory.

### **Human influenza surveillance**

- To keep and enhance actions of the previous stage;
- To review and extend the publicizing of protocol for investigation of suspect cases;
- To enhance surveillance for identifying and investigating outbreaks and/or clusters of severe cases;
- To publicize the warning for companies and schools to decide on absenteeism and to notify municipal, state and federal offices;
- To broadly spread information on which procedures should be adopted in face of a suspect case of infection by a new viral subtype;
- To adopt measures for blocking transmission of the primary case and secondary cases;
- To call the National Civil Defense for jointly evaluation of the need to suspend collective activities.

### **Laboratory**

- To keep and intensify actions of the previous stage.

### **Animal influenza surveillance**



**In development. To be concluded on 10/31/2005**

**Civil Defense**

**In development. To be concluded on 10/31/2005**

**Assistance Network – Basic Care**

**In development. To be concluded on 10/31/2005**

**Assistance Network – Hospital Care**

**In development. To be concluded on 10/31/2005**

**Assistance Network – Hospital Infection Control**

- To keep and enhance actions of the previous stage.

**Immunization**

- To keep, enhance and intensify actions of the previous stage.

**Clinical handling and use of antiviral/antimicrobial agents**

**In development. To be concluded on 10/31/2005**

**Communication**

- announcement of the situation with an epidemic wave warning in the country.
- publicize notices and articles with evaluations of taken measures in previous stages and warning for a new outbreak.
- publicizing of restraint measures.
- intensification of actions of the previous levels.

**Social Mobilization**

**In development. To be concluded on 10/31/2005**

## **CHAPTER 6**

### **Pandemic Period**

In this chapter, we have made priority the activities that should be developed in the pandemic period, which consists of actions activities essential for controlling pandemic and minimizing its direct effects, such as morbidity and mortality rates, including information on use of vaccines and antiviral agents (prophylaxis and treatment), and its indirect effects, such as social rupture. In the pandemic period, all health services, from basic network to high-complexity hospitals, should be prepared to receive and adequately treat infected patients. It is necessary to foresee yet inclusion of alternative services for receiving and treating patients, in case there is saturation of services capacity currently available, as well as training of volunteers for supplying the demand for human resources.

The focus of this chapter is to involve a series of activities that often should be developed in a simultaneous and harmonic way to respond to a pandemic.

The activities will be described in components, such as surveillance, laboratory, basic and hospital care network, use of vaccines and antiviral agents and communication.

### **Stage 7**

This stage represents the dissemination of epidemic in national territory, when actions should be aimed at minimizing morbidity and mortality rates, and the social and economic impact.

#### **Human influenza surveillance**

- To extend the publicizing of the protocol for clinical handling, prophylaxis and treatment with antiviral agents for specific groups;
- To implement simple system of epidemiologic surveillance for monitoring the course of pandemic by municipality, state and region, according to age groups;
- To spread information for general population and for health professionals;
- To collaborate with international organizations and bordering countries;
- To implement, jointly with ANVISA and DAF, protocols of evaluation of antiviral agents resistance.

#### **Laboratory**

- To speed up the supply of reactive agents and raw materials for all instances of the influenza surveillance network (sentinel units, LACEN and LRN) in all Brazilian States, preferably the most affected.
- Implementation of screening measures for diagnosis of Influenza virus new strain, in the first suspect cases, in different regions of the country, wherever occurs a great number of suspects.
- To collect all samples of the first suspect cases of Influenza, in all Brazilian States.
- In special situations and to confirm circulation of a new strain in Brazil, to collect specimens such as serum, bronchial alveolar lavage fluid and lung tissue (including "post-mortem").
- After proving the presence of pandemic strain in Brazil, to collect samples of very severe cases to

confirm the genomic analysis in relation to mutations etc.

- Once proven the circulation of pandemic strain in the country, to promote only the collection of samplings in regions where the virus has manifested, with the purpose of monitoring the viral strain circulation in Brazil.
- To collect samples after use of antiviral agent for behavior analysis of the new strain (whether there is resistance or not) in face of the treatment.

#### **Animal influenza surveillance**

**IN DEVELOPMENT. TO BE CONCLUDED ON 10/31/2005**

#### **Civil Defense**

**IN DEVELOPMENT. TO BE CONCLUDED ON 10/31/2005**

#### **Assistance Network – Basic Care**

- To reinforce jointly with professionals the norms of emergency handling respiratory transmission diseases and on undertaking trials on demand in clinics for referring really severe cases
- Acting on spread of information, orientating the public on contamination risks and ways of avoiding it.
- To keep constant evaluation in risk units in their action areas, such as schools, nursing homes and others
- To help other instances in monitoring the clinical-epidemiologic standard
- To act on non-pharmaceutical interventions.
- To act on execution of vaccination campaign as soon as it is available
- To restructure health services so that they have conditions of meeting the demand, providing reposition of materials and drugs in order for them to be able to provide quality service to users in need, always keeping the staff well informed about treatment and forwarding protocols.

#### **Assistance Network – Hospital Care**

**IN DEVELOPMENT. TO BE CONCLUDED ON 10/31/2005**

#### **Assistance Network – Hospital Infection Control**

- Use of private rooms with negative pressure whenever possible for patients with suspicion of or confirmed influenza. Many hospitals find logistics difficulties and physical limitations when they receive a great number of patients with suspicion of influenza during community outbreaks. If there are not enough private rooms available, you should consider isolation by type (i.e. to separate patients based on type of disease/etiologic agent) or at least avoid sharing rooms with high-risk patients. **(Attachment 4)** discloses the recommended precaution measures, considering transmission by droplets.
- In the pandemic period, there is marked and continuous transmission in the general population, so that all health services should be prepared to receive patients with suspicion of influenza, using adequately the precaution measures disclosed in **Attachment 4**.
- To evaluate national repercussion on the health services capacity (number of beds, isolations etc.), health professionals and use of alternative services.

- To fully apply emergency actions for health services in all levels: additional support of workers and volunteers, to provide medical and extra-medical support for sick people in alternative services and to provide social and psychological support to health professionals, patients and community.

### **Immunization (after making available vaccine against pandemic strain)**

- In the first moment, make these priority:
  - o national authorities,
  - o health workers,
  - o armed forces and civil defense workers,
  - o transportation workers (road ports, airports, borders),
  - o mining and power workers, city cleaning workers, people responsible for water supply, telecommunications, food supply, i.e. everything comprising essential services.
  - o to vaccinate also people with risky clinical conditions (chronic diseases, immunodeficiency, and others).
- Second moment: to vaccinate workers, factory and company employees, public servants.
- Third moment: children and young people, if the circulating strain is N2, due to the circulation that happened before 1968; thus the greatest risk of severe disease would be on people under 36, because they would have no cross-protective immunity if exposed to this strain.  
If the circulating strain is H5, H6, H7 or H9, the risk is equal for all population in relation to severity of disease, because it has not circulated in humans yet. In this case, you should make a priority the workers of essential services so that the country can keep on working.
- To establish negotiations and agreements for buying concentrates or finished products already started with pandemic subtype, for bottling in Brazil (depending on availability);
- To develop strategies and norms for storage, distribution and administration of pandemic vaccine based on already existent references on the vaccine;
- To investigate and follow adverse events temporarily associated to vaccination;
- To evaluate need of extending the vaccination for all direct contacts of detected cases and availability of vaccines for undertaking it;
- To continuously assess the quantity of human resources and the need for extending the development of immunization actions;
- To develop effective mechanisms for mobilizing human resources, capable of responding quickly in vaccinations (primers, informative handbills);
- To strengthen partnerships with PSF, ANVISA, association of retirees in the field of health professionals, for posterior recruitment of human resources for vaccinating the target-group;
- To carry out quick trainings on immunobiological agents preservation and vaccination against influenza for recruited human resources for the immunization actions;
- Elaboration of technical document for vaccination in pandemic and to carry out training of professionals for vaccination;
- To establish technical cooperation jointly with affected bordering countries for application of strategies and quick responses;
- To monitor the vaccine covering and to perform estimation of vaccine effectiveness;
- To define evaluation strategies for the vaccination, assuring adjustment if necessary
- To consider extending of purification that may optimize production, and to seek for agreements

and negotiation to use the installed capacity of Biomanguinhos;

– To ensure distribution of pandemic vaccines for hard-access locations that have no cold chain;

**Clinical handling and use of antiviral/antimicrobial agents**  
**IN DEVELOPMENT. TO BE CONCLUDED ON 10/31/2005**

**Communication**

Action:

- publicizing the national situation
- publicizing criteria of vaccination and antiviral agents use
- intensification of actions of the previous levels

**Social mobilization**

**IN DEVELOPMENT. TO BE CONCLUDED ON 10/31/2005**

**CHAPTER 7**

**Post-Pandemic Period**

In this chapter, we have made priority the activities that should be developed in the post-pandemic period, which consists of actions and activities that involve return to activities of the previous endemic level and organization of activities for repairing the damage caused. Some examples of activities of this chapter: health services network restructuring, deactivating alternative services created for the pandemic and taking advantage of others that might be useful for maintenance of health care and reorganization of activities until there is a new pandemic stage.

**In development. To be concluded on 10/31/2005**

## **CHAPTER 8**

### **Legislation for an influenza pandemic**

**IN DEVELOPMENT. TO BE CONCLUDED ON 10/31/2005**

**BRAZIL'S CONTINGENCE PLAN TO  
CONFRONT INFLUENZA PANDEMIC  
– PRELIMINARY VERSION –  
ATTACHMENTS**

**SEPTEMBER 2005**

## **ATTACHMENT 1**

### **Clinical Aspects of the Influenza**

The influenza or flu is a viral acute infection of the respiratory system, with global distribution and highly transmittable. It starts with sudden fever, myalgia and dry cough. In general, its evolution is self-limited, lasting few days. Its importance is due to its epidemic nature, high morbidity with high rates of hospitalization for elderly or patients carrying chronic debilitating diseases. The early symptoms usually manifested 24 hours after the contact and the individual typically presents fever ( $> 38^{\circ}\text{C}$ ), headache (cephalea), muscle pain (myalgia), chills, prostration (weakness), dry cough, throat ache, sneeze and runny nose (nasal secretion). It may also present hot and humid skin, hyperaemic eyes (eye redness) and watering eyes. Fever is the most important symptom and lasts about three days. The systemic symptoms are very intensive in the initial days of the disease. As it develops, the respiratory symptoms become more evident and usually last for 3 to 4 days, after the fever ceases. Other typical symptoms are dry throat, hoarseness, and retrosternal "burning" sensation when coughing. The clinical condition for healthy adults may vary in intensity. In children, temperature may reach higher levels, and usually presents increased cervical lymph nodes (ganglions on the neck), bronchitis or bronchiolitis, besides the gastro-intestinal symptoms. The elderly almost always have fever, sometimes with no other symptom but, typically, the temperature is not so high.

#### **Etiological agent**

The influenza virus causes the flu. These are single-stranded RNA viruses of the Orthomyxoviridae family, and are subdivided into three types antigenically distinct: A, B and C. The A-type influenza virus is classified according to two surface proteins (Hemagglutinine and Neuraminidase); it may have its structure changed allowing for emergence of new strains, thus contributing to the occurrence of flu epidemics and pandemics. The A-type virus is more susceptible to antigenic variations and, therefore, contributes to the existence of several sub-types, being responsible for the occurrence of most of the flu epidemics. The B-type influenza virus undergoes less antigenic variations and is associated to more centralized epidemics. The C-type influenza virus is antigenically stable, causing sub-clinical diseases and does not cause epidemics; therefore, they deserve less attention in public health.

The B-type viruses occur exclusively in human beings, while the C-type affect humans and pigs, and the A-type affect human beings, pigs, horses, marine mammals and birds.

#### **Transmission**

The influenza virus is transmitted from person to person, mainly by great droplets produced when an infected person coughs, sneezes or talks. In the transmission through the droplet, the infected individual produces great droplets containing the virus ( $> 5\text{ }\mu\text{m}$ ). Such particles do not remain suspended in the air, but cross a short distance (usually 1 meter or less) and are directly deposited on the eye or nasal or oral mucosa of a susceptible individual. Therefore, this kind of transmission requires close contact of the individuals. The influenza virus may also be transmitted by direct contact, which occurs when the skin contaminated with respiratory secretions containing the virus directly contacts other individual's skin (like by kissing or shaking hands) followed by the contact and inoculation of the eyes or nasal or oral mucosa. The transmission may also happen through indirect contact, which occurs when a susceptible individual touches a contaminated object or environment and then touches and inoculates the eye or nasal or oral mucosa. The importance of the role played by the air in the influenza transmission is uncertain. It happens when small residual particles of evaporated droplets ( $< 5\text{ }\mu\text{m}$ ) or dust particles containing the virus remain suspended in the air for long periods



of time. Such small particles may be brought in the air and be inhaled by a susceptible individual who is whether in the same environment or far from the source individual. Therefore, the transmission through the air does not require for close contact person-to-person. The influenza virus' survival out of the body is, on average, 24 to 48 hours on hard and non-porous surfaces, from 8 to 12 hours on clothes, papers and tissues, and 5 minutes on the hands. **(Canadian Plan and Infection Control Guidance: Pandemic Influenza Response – England)**. Although the inter-human transmission is the most common one, the direct transmission of the virus from birds and pigs to human beings have already been documented.

### **Incubation Period**

The typical incubation period is 1 to 4 days.

### **Transmissibility period**

An infected individual may transmit the virus since 2 days previously to the symptoms start, up to 5 days after the symptoms appear. Usually, the first 3 to 5 days after the symptoms start for adults, and over 7 days for young children. **(Canada Plan)**. Transmissibility may increase depending on the disease seriousness and temperature rise. The transmissibility period may be shortened in patients subject to anti-viral therapy, and may be expanded for children and immunodepressed individuals. Since approximately 50% of the infections by influenza are asymptomatic, the infected individual may transmit the virus even if they do not present the symptoms. **(Infection Control Guidance: Pandemic Influenza Response – England)**.

### **Complications**

Typically, the complications occur in the elderly and debilitated individuals. The risk situations include chronic pulmonary disease (Asthma and Chronic Obstructive Pulmonary Disease COPD), cardiopathies (Chronic Cardiac Insufficiency), chronic metabolic disease (diabetes, for example), immunodeficiency or immunodepression, pregnancy, chronic kidney disease and hemoglobinopathies. The most usual pulmonary complications are the secondary bacterial pneumonias, where the most frequent are those caused by the following agents: *Streptococcus pneumoniae*, *Staphylococcus* and *Haemophilus influenzae*. For immunocompromised individuals the clinical condition uses to last longer and be more serious. Pregnant women with influenza during the second or third quarters of pregnancy are more subject to hospitalization. Among the non-pulmonary complications in children the Reye's Syndrome stands out, being also associated to chickenpox. This Syndrome is characterized by encephalopathy and fatty liver degeneration, after using the acetyl-salicylic acid during one of such viral conditions. Therefore, it is recommended to avoid using medications with this substance in the composition for the symptomatic treatment of the Flu Syndrome or Chickenpox in children. Other complications include Miositis, Miocarditis, Pericarditis, Toxic Chock Syndrome, Guillain-Barré's Syndrome and, more rarely, Encephalitis and Transversal Myelitis.

### **Laboratorial Diagnosis**

The adequate procedures for collection, transportation, processing and storage of clinical species are crucial for the diagnosis of viral infection. The preferential specimen for laboratorial diagnosis is the nasopharyngeal secretion obtained through nasopharyngeal aspiration assisted by a disposable collector or through combined swab (an oral and two nasal ones). These samplings are to be collected preferably until the fifth day after the symptoms start, and transported in recyclable ice to the laboratory for the due processing and cannot be frozen. The influenza diagnosis is characterized by means of indirect

immunofluorescence (IF) techniques and/or by isolation of the agent in cell cultivations or embryos (considered the standard method). The antigenic and genetic characterization of the virus is made employing the hemmagglutination-inhibition assay and molecular biology techniques, respectively.

### **Differential diagnosis**

The influenza differential diagnosis should take into consideration a broad range of acute respiratory infections of viral etiology. Among them, are outstanding those caused by the Sincial Respiratory Virus (SRV) and by the Adenovirus. In the infection by influenza, the systemic symptoms are more intense than in the other syndromes. However, in several instances the differential diagnosis only through the clinic condition may be hard to make.

## **ATTACHMENT 2**

### **Manual of Rules and Procedures for the Influenza Diagnosis**

Along the last few years, new and simple laboratory techniques have been systematized, allowing for directly proving the presence of viral antigens in respiratory secretions. These diagnosis methods have some advantages when considering that:

- a) They allow for quickly identifying the virose (few hours after collecting the specimen for examination), thus inducing to the establishment of preventive measures against the agent dissemination.
- b) The confirmation of the viral etiology may avoid the unnecessary administration of anti-biotic drugs.

Among the techniques for quick diagnosis currently available, the indirect Immunofluorescence – IFI has proved to be the most suitable for investigating the viral etiology in cases of acute respiratory infection. Compared to other pattern procedures, it is also considered the most adequate method for small-size laboratories.

In this manual we present practical indications for using a commercial kit (CHEMICON) aimed at the immunofluorescence-based laboratory diagnosis of respiratory viruses.

#### **Method**

The immunofluorescence (Fig. 1) involves the employment of a monoclonal antibody that specifically jointed to the antigen – virus – object of the assay results in the formation of an antigen-antibody complex. Later, this complex is added with an anti-immunoglobulin marked with a dye – isothiocyanate of fluorescein. If the reaction is positive, it will show the presence of fluorescent cells when observed in a fluorescent microscopy.

#### **Clinical Specimen Collection**

A successful diagnosis depends basically on the quality of the clinical specimen collected, its adequate transportation and the storage conditions previously to the laboratory processing. The method sensitiveness is also influenced by the specificity of the reagents employed and by the technical experience of the professional responsible for the assay.

Preferably, the clinical samplings for the diagnosis of viral infections in the upper respiratory system are: aspirated nasopharyngeal – ANF – or combined swabs (nasal / oral), obtained no later than three days after the symptoms started appearing – the acute stage of the disease. Regardless the nature of the specimen, it should be obtained in compliance with the biosecurity rules (use of disposable gloves, mask and lab coats).

#### **Required material**

- a) Portable aspiration pump High volume vacuum pressure pump# XX56 000.00 MILLIPORE.
- b) Disposable plastic collector of secretion (20cc) coupled with probe (number 6 1/2) and with vacuum control Argyle (Sherwood-Medical) Cat. # 8888-157386.
- c) Serum equipment for parenteral administration.
- d) Viral\* transportation medium.
- e) Urethral plastic probe n ° 6 sterilized.
- f) Disposable sterilized swabs (15 cm), individually packed, to collect clinical specimens. Polyester fiber-tipped applicator. Falcon Cat. # 2069.
- g) Disposable polypropylene tubes (17x119mm) transparent (15 ml) with Polyethylene Caps. Corning.

### Aspirated nasopharyngeal (ANF)

The ANF collection is a non-painful process which can cause only watering eyes. Disposable plastic collectors of mucus (Fig. 2) or serum device coupled to a probe (Fig. 3) are preferably recommended to obtain the specimen. The recommended probe is the urethral nº 6 with one single orifice on its end. The probe size is variable, according to the manufacturer, and priority should be placed on the more flexible ones. The aspiration may be made using a portable aspiration pump or hospital wall vacuum; do not use too strong vacuum pressure.

\* Solution of preservation and transportation medium for clinical species.

It is recommended to use Hanks' solution, cells cultivation medium or triptose-phosphate broth supplemented with protein for the viral stabilization, such as V-fraction bovine serum, gelatin or glycerol in a final concentration of 0,5-1%. The anti-biotic addition (1600 U/mL of penicillin and 800 ug/mL of streptomycin) and antifungal (10Ug/mL of fungizone) is recommended to avoid the proliferation of bacteria and fungus. If there is no adequate PBS ph 7.2 transportation medium, one can exceptionally employ it added with protein, anti-biotic and antifungal.

During the collection, the probe is introduced through the nostril until it reaches the nasopharyngeal region, when the vacuum is applied and aspirates the secretion into the collector or device (Fig. 4). This procedure should be made on both nostrils, keeping the probe movement to avoid the direct pressure over the mucosa which could cause some bleeding. One should alternate the collection on both nasal cavities until reaching sufficient volume of ANF, i.e., approximately 1 ml. The quantity of secretion to be collected will depend on the IRA etiology, the development stage of the clinical condition and the patient's hydration level. Patients with fever present thick secretion. After the nebulization with physiological serum the secretion is more fluid and abundant and therefore is more easily obtained. Do not insist if the collection does not reach the desired volume (+/- 1ml) otherwise you can damage the mucosa.

After been collected, the ANF shall be forwarded to the laboratory, in individual plastic bag, sealed and duly identified, labeled with the patient's name, the specimen nature, the collection data and the patient's clinical record.

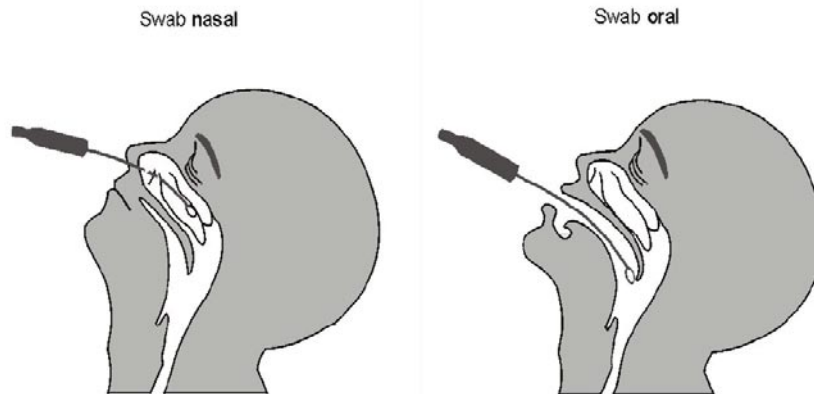
The specimen shall be transported to the laboratory on the same day of the collection, in a styrofoam box with ice. Exceptionally, the aspirated specimen may be stored and preserved at 4°C – do not freeze it – for no longer than 24 h.



Fig. 4 – Aspirated nasopharyngeal

- Combined oral/nasal Swab.

Collect (Fig.5) three swabs (one from the oropharynge and the other two from each nasal cavity). Then, insert the s in the same bottle with three milliliters of transportation medium (please refer to the specification attached), close and duly identify the bottle. The swabs' conservation and transportation should follow the recommendations for the ANF.



### Laboratory processing for clinical specimens

Before processing the specimen, verify if it has been adequately collected and transported to avoid false results.

#### Required material

- Acetone P.A ( $C_3H_6O$ ).
- 5 Liquid nitrogen bottle.
- Diagnosis kit Respiratory Panel 1 viral screening & identification kit. CHEMICON Cat. # 3105.
- Lamina for immunofluorescence microscopy (26 mm x 76 mm) extra thin, delimited with 10 circles, lapidated and with an opaque end. Perfecta.
- Disposable transference plastic pipettes Pasteur-type, 15 cm in length, marked off and with total capacity of 7 ml.
- PBS pH 7.2 Taylor Wharton Cryogenics.
- Sterilized polypropylene tubes (12,7 x 76,5 mm), 4 ml, with caps, flat basis for transportation and freezing of specimens (cryo tubes). Corning.
- Disposable transparent polypropylene tubes (17 x 119 mm), conic, (15 ml), with caps. Falcon Cat. # 2097.

#### After the aspirated nasopharyngeal

- With a disposable transfer pipette, or Pasteur-type, transfer the ANF from the collector or device to a conic tube (17 x 119 mm), previously identified.
- Add 3 ml of transportation medium (see the specification). Make successive pipette aspirations to homogenize the mixture and release the epithelial cells from the mucus.
- Centrifuge at 1.000 rpm for 10 minutes.
- Transfer the floating to the cryo tube, previously identified, and storage it in a liquid nitrogen bottle or freezer at  $-70^{\circ}C$  for further efforts to cultivate the virus.
- Suspend the cell sediment in 3-5 ml of PBS and centrifuge once again at 1000 rpm for 5-10 minutes.
- Remove the floating and once more suspend the cell sediment in PBS. Depending on the quantity of cells obtained, add such a quantity of PBS enough for obtaining a translucent suspension.

- g) Clean the lamina with acetone and identify it with the patient's name and identification number.
- h) Put one drop (15 to 20  $\mu$ l) of the cell suspension in areas (circles) previously defined on the lamina. Prepare two laminas for each specimen, one with 2 and the other with 8 circles. Depending on the quantity of suspension obtained, it is advisable to prepare additional laminas for complementary analysis.
- i) Dry the lamina with hair drier (cold air), domestic fan or in a laminar flow cabinet.
- j) Immerse the lamina for 10 minutes in cold acetone to fix the preparation.
- k) After the fixing and drying, the lamina may be stored in a refrigerator (4°C) for up to 72 hours before it is processed in IFI assay. Alternatively, the laminas may be stored at -20°C for several months on in a freezer -70°C for over one year.

### **After the combined oral /nasal swabs**

- a) Shake the tube containing the swabs in a vortex-type shaker.
- b) With round movements, press the swabs against the tube wall to drain the remaining fluid. Dispense the swabs and centrifuge the suspension for 10 minutes at 1000 rpm.
- c) Follow the procedures described in items "d" to "j".

### **Indirect immunofluorescence assay**

Follow the instructions provided in the diagnosis Kit Respiratory Panel 1 viral screening & identification kit (Fig. 6)

### **Required material.**

- a) Distilled water (200 ml).
- b) Diagnosis kit Respiratory Panel 1 viral screening & identification kit. CHEMICON Cat. # 3105.
- c) Laminulas 24 x 60 mm. Corning, Cat. # 583331.
- d) Immunofluorescence microscopy.
- e) PBS pH 7.2.

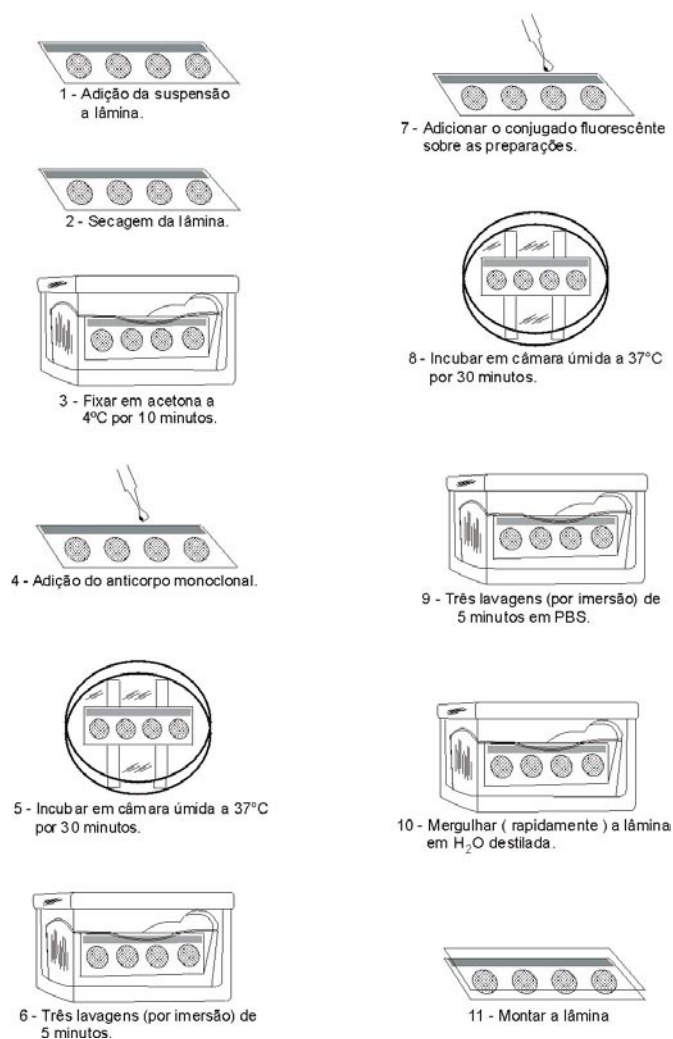
### **Procedure**

- a) Remove the diagnosis kit from the refrigerator for it to adapt to the ambient temperature.
- b) Take the lamina (containing the fixed cell suspension) from the refrigerator or freezer -70°C and let it dry at the ambient temperature.
- c) Put the lamina in a wet chamber (plastic box with the bottom coated with moisture towel paper).
- d) Add a drop (15 to 20  $\mu$ l) of the different monoclonal anti-bodies (screening, adenovirus, influenza A, influenza B, parainfluenza 1, parainfluenza 2, parainfluenza 3, sincial respiratory virus and normal mouse antibody) to different circles on the lamina.
- e) Incubate at 37°C for 30 minutes so that the antigen-antibody reaction occurs.
- f) Wash the lamina 3 times (immersion) in PBS, for 5 minutes each time.
- g) Put the lamina on the vertical, on a towel paper sheet, to drain\* the excess of PBS.
- h) Add a drop of the conjugated (anti-mouse IgG / isothiocyanate of fluorescein) to each circle on the lamina.
- i) Incubate the lamina in the wet chamber at 37°C for 30 minutes.
- j) Wash the lamina again in PBS, for 3 times of 5 minutes each.
- k) Quickly immerse the lamina in distilled water.
- l) Repeat the stage (g).
- m) Add a drop of the montage fluid on the center of the lamina.

- n) Carefully put one laminula on the lamina, avoiding air bubbles between the two surfaces.  
o) Use the immunofluorescence microscopy with a 40x objective and 10x ocular lens.

\* After adding the monoclonal antibodies, the lamina should never be dry, in any stage.

Fig. 6 - Etapas de execução do teste de imunofluorescência indireta.



- Fig. 1 - Addition of the suspension to the lamina.  
Fig. 2 - Lamina drying.  
Fig. 3 - Fixation in acetone at 4° for 10 minutes.  
Fig. 4 - Addition of the monoclonal antibody.  
Fig. 5 - Incubation in wet chamber at 37°C for 30 minutes.  
Fig. 6 - Wash it by immersion 3 times of 5 minutes each.  
Fig. 7 - Add the fluorescent conjugate on the preparations.  
Fig. 8 - Incubation in wet chamber at 37°C for 30 minutes.  
Fig. 9 - Wash it by immersion in PBS 3 times of 5 minutes each  
Fig 10 - Quick immersion of the lamina in distilled water.  
Fig 11 - Assembling the lamina.

## Interpretation of the results

The lamina is expected to exhibit at least three cells for each field in order to be suitable for detection. An insufficient number of cells may lead to false-negative results.

Fluorescence is recognized of its intense green-apple color, always in the cell. The color pattern uses to be granular but great inclusions may be homogeneously dyed. Any extra-cell color or fragments of cells showing fluorescence should be considered as non-specific. Three or more intact cells disclosing a specific pattern of fluorescence may be accepted as a positive reaction.

<b>Virus or group of viruses</b>	<b>Fluorescence pattern</b>
<b>Influenza</b>	The fluorescence may be present only in the nucleus or cytoplasm, or in both.
<b>Parainfluenza</b>	The fluorescence is cytoplasmatic, with aspect of thin granules.
<b>VRS</b>	The fluorescence is totally cytoplasmatic. Corpuscles of inclusion and thin fluorescent particles may be present.
<b>Adenovirus</b>	The fluorescence for adenovirus is variable, usually consisting of a nuclear and cytoplasmatic fluorescence.

The negative pattern is evidenced by the lack of specific fluorescence and the prevalence of a red color in the cells, because of the presence of the Evan's blue in the conjugate.

## Limitations

As aforementioned, the quality of the clinical specimen is extremely important for successfully executing the assay. The epithelial cells infected with virus are extremely unstable and, therefore, may be easily damaged in the event of inadequate handling or delayed processing. Furthermore, it is very important that the clinical samples to be submitted to the IFI techniques are to be immediately refrigerated after the collection and should remain in that temperature until they are processed. The specimen centrifuging should not be higher than 1000 rpm, under the risk of injuring the cells to be examined.

The number of infected cells that may be obtained through aspiration or swabs decreases along the infection. Therefore, the specimens are to be obtained as early as possible after the symptoms appear, preferably during the 3 first days of the disease.

## Quality Control

Each kit includes laminas with infected and non-infected cells, to be used as appropriate control of the monoclonal and conjugate used. It would be advisable for the laboratory to kept the patient's lamina stored at -70°C for further quality control of reagents and procedures used.



### **ATTACHMENT 3**

#### **Recommendations for laboratories' conduct and biosafety rules**

General orientations on biosafety concerning the approach of patients suspect or confirmed, and for the handling of clinical specimens related to such cases.

##### **Necessary care for patients suspected of having been infected with Influenza:**

The patients characterized as suspect cases shall wear mask N95 until the possibility of infection with the influenza virus is excluded.

The hygienization of hands is the most important measure for preventing the dissemination of infections, including those of respiratory transmission.

The hygienization of hands, with water and soap or using an alcohol-based antiseptic solution should precede the use of gloves.

The hands shall be washed, as explained above, every time one undresses the gloves.

##### **Handling of biological samples:**

For all patients suspicious of influenza, samples of nasopharyngeal secretion shall be collected, as described in the Manual of Rules and procedures for the laboratory diagnosis through indirect immunofluorescence (to be published), by CGLAB/SVS/MS.

If it is not possible to obtain the ANF sample, one can collect samples through combined nasal/oral swabs. These are to be immediately put in the viral transportation medium triptose-phosphate broth or in solution PBS pH 7,4. The tubes containing the swabs are to be refrigerated at 4°C until their delivery at the laboratory. These samples must be forwarded to the laboratory on the same day, to be processed.

When the first cases suspicious of infection with the pandemic strain are detected, it is advisable to collect the ANF or swabs samples and, simultaneously, samples of serology (3 ml), with a 15-day interval between the 1st and the 2nd sample, within the first 5 (five) days with the symptoms. If the patient has presented the symptoms for more than 10 days, one single 3 ml collection will be enough. The serums are to be refrigerated at 4°C or frozen at -20°C until they are delivered at the laboratory.

##### **Individual Protection Equipment (IPE) for the health professional in charge of the collections:**

- Disposable Lab coat, waterproof, long sleeved with cotton or elastic cuffs, opened in the back (weight 50 g/m2).
- Disposable latex gloves, non-sterilized (gloves for non-surgery procedures). Put two gloves on each hand and dispose them immediately after use, according to the safety rules.
- Face protection mask, respirator type, for particles, with no maintenance, with minimum filtering efficacy of 95% of particles up to 0,3µ (N95, N99, N100, PFF2 or PFF3 Masks). Masks with special valves for facilitating breathing are allowed.
- Bonett.
- Eyeglasses.
- Wash the hand previously and after the collection, as described in Attachment 4.

##### **IPE for the laboratory professional who will handle the samples:**

All the above-mentioned recommendations are applicable to this item.

It is recommended the continuous use in the laboratory of, at least, class 2 biological contention cabinets for handing samples collected from patients suspicious of influenza.

All the individual protection materials are to be properly packed and the IPE should not be reused.

Note: It is necessary to clean the rooms and the work team, pursuant to the recommendation in **Attachment 4**.

**De-contamination:**

Protects the responsible for collecting the sample, the patient, those who transport the material, the laboratory staff and the community.

**On the material used for collection and diagnosis:**

The material used must be de-contaminated.

**Disposal of the clinical specimen used for the diagnosis:**

The disposal of the clinical specimen shall receive the following treatment.

Moreover, it is advisable to make the chemical disinfection of the work surface, using sodium hypochlorite.

## **ATTACHMENT 4**

### **Infection Control in Health Services**

#### **A) Hands hygienization**

- The health professionals, patients and visitors should be duly instructed and monitored concerning the importance of hands hygienization.

– Before and after having direct contact with patients with influenza, their belongings and the surrounding environment, as well as when entering or leaving areas with infected patients, it is necessary to wash the hands and use antiseptic products.

The influenza virus is rapidly inactivated in 30 seconds after the hands' antisepsis with alcohol at 70%. **(Schurmann W, 1983)**

#### **B) Hygienic measures**

Patients, health professionals and visitors should be oriented towards minimizing the disease transmission risks by practicing hygienic measures, using facial tissues for nasal hygiene, covering the mouth and the nose when coughing or sneezing, and keeping the hands off from the eye's and nose's mucosa.

#### **C) Individual Protection Equipment**

##### **1) Masks**

The masks are to be used when dealing with patients who are supposedly or confirmedly infected with the influenza. The use of masks is important to prevent the transmission of other agents when serving patients with undiagnosed cough. Masks and eyeglasses (or face shield) shall be used to prevent the exposure of the professionals to the splashing of blood, body secretions and excretions. The health professionals are to be instructed to avoid touching their eyes with their hands, thus avoiding self-contamination. In procedures with risk of generating aerosol, use the N95 mask. For example: intubations, nasopharyngeal aspiration, tracheotomy, respiratory physiotherapy, bronchoscopy and autopsy involving pulmonary tissue. Whenever possible, the procedures with generation of aerosol shall be performed only in restricted areas, with no other patients present. **(Pandemic Influenza Action Card – Standard Infection Control Precautions – England)**

##### **2) Gloves**

– The gloves are to be used whenever exists the possibility for the professional to have contact, through the hands, with blood, body fluids, secretions, excretions and mucosa, to reduce the chance of virus transmission from infected patients to the professional, and from patient to patient as well, through the professional's hand. Professionals with open wounds in the hands must use gloves when providing direct assistance to the patients.

– Hands hygienization is crucial, even when using gloves.

– The gloves should not be reprocessed for reuse.

##### **3) Laboratory coat**

- The professionals should wear long sleeved laboratory coats to protect their skins and avoid dirtying the clothes during procedures that are likely to generate splashing of blood, body fluids, secretions and excretions.
- The health professionals shall make sure that eventual skin lesions on the arms are covered with dry clothe.

## **D) Cleaning, disinfection and sterilization of medical articles**

The articles are products for health and comprise objects, equipment, tools, utensils (bedpans, etc.), accessories and others. The articles may be classified according to the risk of infection transmission as critical, semi-critical and non-critical, and its processing is defined according to its classification, characteristics and the manufacturer's recommendations.

The sequence steps for processing articles are as follows: cleaning, disinfection and/or sterilization and storage, according to the purpose of each article.

The articles used for penetration through the skin and surrounding mucosa, sub-epithelial tissues and vascular system, as well as any other related to this system, are called CRITICAL ARTICLES. They must be sterilized in order to fulfill their intended purposes.

The articles for contact with injured skin or non-injured mucosa are called SEMI-CRITICAL ARTICLES and are subject to high-level disinfection or sterilization to guarantee the quality of their multiple uses.

The articles for contact with the patient's non-injured skin are called NON-CRITICAL ARTICLES and require low- or medium-level cleaning, depending on their intended use or their latest use.

Whenever possible, the equipment for the care of patient with influenza should be used exclusively by that patient, like stethoscopes, sphygmomanometer and thermometers. Such equipment must be cleaned and disinfected before being used with other patients. The health professionals should ensure that no equipment or article is used for other patient without have been duly cleaned and reprocessed. They are also expected to ensure that the surfaces have been adequately cleaned and disinfected before releasing the ambient for another patient.

The handling of articles and surfaces require the use of IPE/CPE (gloves, laboratory coat, masks, boots, protection eyeglasses and others) adequate to the nature of the risk to which the hospital and cleaning staff is exposed.

There is no special precaution measure for foodware, like dishes, glasses, cutlery and trays used by individuals infected by the influenza virus, since the combination of hot water and detergent that is used is enough to inactivate the pathogens. Furthermore, disposable utensils may be used.

## **Cleaning**

Cleaning is the process aimed at removing the visible dirt (organic and inorganic) and, therefore, the removal of most of the microbial charge. It is a crucial and necessary stage for reprocessing all medical-hospital articles and equipment.

For the mechanical cleaning, the following methods may be employed, according to the characteristics of the articles:

- By rubbing brushes and using cleaning solutions;
- Developed through equipment items like: ultra-sonic washing machine, sterilizing and disinfecting

washing machine, thermal disinfecting washing machine and discharge washing machine.

The cleaning process steps are: gather by kind of article; immerge or soak in solution; clean, rinse with drinkable water; rinse with deionized or demineralized water; and dry.

The cleaning execution may employ enzymatic cleaners, detergents and exfoliating solutions (SOBECC 2005).

Depending on the article's use, it should be stored or subject to disinfection or sterilization.

## Disinfection

Disinfection is the process of eliminating or destroying microorganisms (whether pathogenic or not), in their vegetative form and present in the inanimate articles and objects, by applying physical or chemical agents named sanitation products, capable of destroying in an operational time span of ten to thirty minutes (Brazil, 2001).

To disinfect articles and equipment suspected of contamination by influenza, it is recommended:

- High-level disinfection: it destroys all vegetative bacteria, micro-bacteria, fungus, viruses and part of the spores. It is indicated for articles such as laryngoscope laminas, respiratory therapy equipment, anesthesia devices and flexible fiber endoscope device. The agents typically employed are the glutaraldehyde and the peracetic acid, additionally to the pasteurization process;
- Intermediary-level disinfection: it is virucide, bactericide for vegetative forms, including the tuberculosis bacilli. It does not destroy spores. The most used compounds are formulations containing chlorine, iodophores, phenolics and alcohols; and,

The disinfection may employ the following methods:

- Physical process: comprises the exposition to physical agents such as temperature, pressure and electromagnetic radiation, wet heat or, preferably, automatic mechanic systems, with pressure of water jets at temperatures ranging from 60oC to 90oC, for 15 minutes, like the high-pressure sanitation washing machines, thermal disinfecting washing machines and similar (Brazil, 1994).
- Chemical process: stands for the use of chemical products with the following active substance, pursuant to the Directive n. 15, of 23 August 1988, by the Ministry of Health (Brazil, 1988): aldehydes (formaldehydes and glutaraldehyde), phenolics, quaternary ammonium, organic compounds that release active chlorine, inorganic compounds that release active chlorine (sodium hypochlorite), alcohols and peroxides.

## Legislation for Sanitation Products:

	Aldehydes	Phenol	Quaternary ammonium	Chlorine inorganic	Chlorine organic	Iodine and derivatives	Alcohols and glycolic	Biguanides
General use	x	x	x	x	x	x	x	x
Lactarium		x	x	x				x
Surfaces	x	x	x	x	x	x	x	x
Semi-critical articles	x	x	x	x	x	x	x	x
Critical articles	x	x	x	x	x	x	x	x

Directive n° 15, of 23 August 1988 / Ministry of Health.

Directive n° 122, of 29 November 1993 / Ministry of Health.

## **Sterilizing**

Sterilizing stands for the process capable of eliminating any form of microbial life, including bacterial spores. An article is considered sterile when the probability for the microorganisms contaminating it to survive is lower than 1:1.000.000. **(Graziano; Silva; Bianchi, 2000).**

An article can be sterilized by means of the following methods:

- Physical process: saturated steam under pressure (ex: autoclave); sterilization by dry heat (ex: stove) ; or sterilization by cobalt 60;
- Physical-chemical process: sterilization by low-temperature steam and gas formaldehyde (VBTF); by ethylene oxide (ETO) or by the hydrogen peroxide plasma;
- Chemical process: by peracetic acid or glutaraldehyde.

## **E) Environment Control**

The fixed surfaces (floors, walls, roofs, doors and knob, furniture, equipment and other installations) represent a significant risk of influenza transmission in the hospital environment.

There are environments, surfaces and furniture that may be a risk of contamination to the patients, hospital staff and visitors, due to the presence of excreta, secretion or exudation of organic material. These places must be decontaminated, whether previously or simultaneously to the cleaning.

It is necessary to disinfect walls, corridors, floors, roofs, windows, doors, in the case of splashing or deposition of organic material of a patient supposedly or confirmedly infected.

## **Cleaning**

Cleaning in isolation areas for influenza shall be concurrent, prompt and terminal.

For the bedrooms of patients with influenza (supposedly or confirmedly) the following procedures are recommended:

Concurrent cleaning, which is done on an everyday basis and includes all horizontal surfaces (floor, equipment and furniture), bathrooms and sinks, freezers, refrigerators, etc., using anti-microbial detergent and, if there is no such detergent, using the ordinary detergent adequate to the nature and use of such surfaces. The procedure is to be mainly done on the places that are most touched or which are nearby the patient's bed, since these sites are more likely to present droplets.

The terminal cleaning is on the event of patient's release, death and transfer. This cleaning is more restricted to the patient's unit and to the items he/she used: bed, mattress, armchair, chair, night tables, etc.

Prompt cleaning is indicated when the environment and equipment are contaminated by the presence of organic material and is to take place immediately after the environment or equipment is dirtied.

The surfaces with organic material shall be disinfected or decontaminated locally and, later, the entire surface must be cleaned using water and soap, with or without using machines.

### **Decontaminations**

Decontamination shall be made as follows:

- Apply the product on the organic material and wait for the time recommended by the manufacturer;

- Remove the decontaminated content using absorbent paper (wearing gloves);
- Dispose on the adequate site and
- Carry out the usual cleaning, with water and soap, on the remaining surface.

## Disinfection

The disinfection of contaminated surface and environment shall be as follows:

- Using gloves, remove the contaminating load using absorbent paper;
- Dispose the paper in a plastic bag;
- On the affected area, apply the adequate disinfectant and let it rest for the time recommended by the manufacturer;
- Remove the disinfectant with moisten cloth and
- Make the cleaning with water and soap on the remaining surface

	Characteristics	Concentration for use	Indications	Counter indication
<b>Alcohol</b>	<ul style="list-style-type: none"> <li>- Bactericide, fungicide and virucide action</li> <li>- The isopropyl alcohol is less effective against virus</li> <li>- Easily applicable</li> <li>- Immediate action</li> </ul>	70% - Friction for 30' until it evaporates	- Furniture in general	<ul style="list-style-type: none"> <li>- Opacity to acrylic materials</li> <li>- Dries plastic and rubber</li> <li>- Inflammable and volatile</li> </ul>
<b>Phenolic compounds</b>	<ul style="list-style-type: none"> <li>- Good results against vegetative bacteria and most of the viruses and fungus</li> <li>- More active in neutral PH</li> <li>- Residual action</li> <li>- May be associated to detergents</li> <li>- Follow the manufacturer's instructions</li> </ul>	- Furniture in general	<ul style="list-style-type: none"> <li>- Furniture in general</li> <li>- Fixed surfaces</li> </ul>	<ul style="list-style-type: none"> <li>- Toxic for the skin and to the Newborn Baby</li> <li>- Environmental pollutant</li> <li>- May become inactive in the presence of organic material</li> </ul>
<b>Quaternary ammonium</b>	<ul style="list-style-type: none"> <li>- Fungicide, bactericide and virucide. It is not tuberculocide neither works against hydrophilic viruses.</li> <li>- Low level</li> <li>- Little corrosive</li> <li>- Low toxicity</li> </ul>	- Several concentrations, according to the manufacturer	- Fixed surfaces, including nutrition and neonatal environments	<ul style="list-style-type: none"> <li>- Low toxicity level</li> <li>- Environmental pollutant</li> <li>- May become inactive in the presence of organic material</li> </ul>
<b>Inorganic chloride</b>	<ul style="list-style-type: none"> <li>- Broad-spectrum</li> <li>- Liquid</li> <li>- Fast action</li> <li>- Low cost</li> </ul>	- Disinfection: 0,02 % to 1% Time of action: 10' - Decontamination: 1% Time of action: 10'	<ul style="list-style-type: none"> <li>- Fixed surfaces</li> <li>- Respiratory therapy materials</li> <li>- May be used as decontamination agent</li> </ul>	<ul style="list-style-type: none"> <li>- Instable: by sunlight, T higher than 25°C and pH.</li> <li>- May become inactive in the presence of organic material</li> <li>- Corrosive for metals and cotton and synthetic clothes</li> <li>- Unpleasant odor</li> <li>- Irritability in the eyes and mucosa</li> <li>- Environmental pollutant</li> </ul>
<b>Organic chloride</b>	<ul style="list-style-type: none"> <li>- Broad-spectrum</li> <li>- Powder, more stable than the Cl-Inor</li> </ul>	- Practical for absorbing liquids - Decontamination: 1,8% a 6% Time of action: 10'	- Decontamination of surfaces	<ul style="list-style-type: none"> <li>- Same problems faced by the inorganic chloride</li> <li>- Activated in the presence of organic material</li> </ul>

- The health care facilities shall follow the legal provisions, mainly concerning laundry and the treatment of residues, as described below:
- Resolution RDC nº 50, of 21 February 2002, dealing with the Technical Regulation for programming, elaborating and assessing physical projects of health care facilities (available at <http://e-legis.bvs.br/leisref/public/home.php>).
- Resolution RDC nº 306, of 07 December 2004, dealing with the Technical Regulation for handling medical waste (available at <http://e-legis.bvs.br/leisref/public/home.php>).
- Manual of Hospital Laundry– MS ( insert reference)

## **F) Isolation**

- During the pandemic warn period, the reference hospitals should be used to refer the patients with respiratory symptoms compatible to influenza, coming from affected countries. These hospitals should be organized and equipped to provide private rooms with negative pressure. The patients with suspect of influenza shall remain in respiratory isolation until the influenza diagnosis is discharged or until the transmissibility period ends. The influenza virus is transmitted during the entire time of duration of the disease, while the symptoms persist. An infected individual may transmit the virus in a period from 2 days before the symptoms start to 5 days after them. Usually, the first 3 to 5 days after the symptoms start for adults and above 7 days for young children (Canada Plan).
- During the pandemic period, many hospitals are likely to face logistical difficulties and physical limitations to receive a huge number of patients with suspect of influenza. If there is not enough private rooms available, they should consider the isolation by group (i.e., separate the patients by kind of disease/etiologic agent). If there are too many patients infected, the hospital should define a specific area for isolation for influenza. Whenever possible, this area should:
  - Have a reception / hospitalization desk in separate for patient
  - Have entry and exit doors separate from the remaining hospital.
  - Restrict the passage of other patients, visitors or professionals who are working in other areas of the hospital.
  - Be previously assessed by the hospital engineering sector to exclude the possibility of the hospital ventilation system convene the air from isolation areas to other areas in the hospital.
  - Place warning signals on the entrance of the influenza isolation area and adopt the necessary measures to allow for the entry in this area.
- The health professionals working in the direct assistance to patients should be organized in shifts to work in influenza isolation areas, or in areas that receive patients with other kinds of pathology, and should not circulate from an area to another.
- Avoid transporting patients with suspected or confirmed influenza. If the patient really needs to leave the room, he/she shall also use a mask.

## **G) Other measures**

- Suspend elective hospitalizations (surgery and clinical).
- Restrict cardiac and pulmonary surgeries.
- Restrict the entrance of visitors with acute respiratory disease.
- Restrict the work of health professions with acute respiratory disease.



## **ATTACHMENT 5**

### **Effectiveness of vaccine against influenza**

In healthy adults, the detection of protector antibodies takes place from one to two weeks after the vaccine. The maximum peak of antibodies happens after 4 to 6 weeks. In order to obtain the maximum success with the use of the vaccine it would be necessary to vaccinate during the period previously to the major viral circulation, provoking the coincidence between the maximum peak of the immunological response (antibody formation) and the maximum peak of the influenza virus circulation (winter). It is worth observing that the vaccine does not prevent the disease in 100% of the individuals inoculated (i.e., some vaccinated individuals will get influenza, despite having been vaccinated). And many individuals may contract the disease by other strains and respiratory viruses, thus mistakenly leading to the impression that the vaccine was ineffective. However, the major importance of the vaccine rests on its power of reducing the risk of the serious complications resulting from the influenza, such as pneumonias and, above all, deaths. Therefore, this is the major purpose of vaccination for the older population **(Brazil, 2005)**.

The protection granted by the vaccine reaches from 67% to 92% of the healthy individuals under 65 years old, depending on the similitude between the strains in the vaccine and the selvage circulating virus. The vaccine effectiveness against influenza depends mainly on the age and immunocompetence of the vaccine receptor. Most of the vaccinated children and young adults develop high post-vaccination titles of antibodies inhibitors of hemmaglutination **(La Montagne, 1983 and Oxford, 1979)**. Even when the vaccine eventually fails in presenting maximum protection in prevention -- what has been observed among the institutionalized elderly -- several studies disclose its impact on the reduced frequency of the number of complications, hospitalizations and deaths.

Some studies have also evidenced that children vaccination results in reduced incidence of otitis media, as well as decreased consumption of anti-biotic drugs **(Clements, 1995 and Heikkinen, 1991)**. With the emergence of new studies providing the benefits of the universal vaccination, the immunization in healthy children of young age is gradually increasing and some countries are increasingly using the vaccine (Izurieta, 2000, CDC, 1997 and McIntosh, 2000). However, nowadays the vaccine is licensed only for children of six months or more. In older people and carriers of chronic diseases the induction of antibody levels is typically lower. However, despite that the vaccine provides an important protection against complications (from 30% to 70%) **(Neuzil, 2000 and Murphy, 1996)**. In institutionalized individuals, the protection against hospitalization and pneumonia ranges from 50% to 60% (Nichol, 1998), and is greater if compared to the occurrence of deaths (80%) **(Toniolo Neto, 2001)**.

## **ATTACHMENT 6**

### **Composition of the vaccine against influenza in Brazil, 1999 to 2005**

1999	A/Sydney/5/97 (H3N2) A/Beijing/262/95 (H1N1) B/Beijing/184/93
2000	A/sydney/5/97 (H3N2) A/New Caledonia/20/99 (H1N1) B/Beijing/184/93
2001	A/Moscow/10/99 (H3N2) A/New Caledonia/20/99 (H1N1) B/Sichuan/379/99
2002	A/Panama/2007/99-Resvir-17 (H3N2) A/New Caledonia/20/99-IVR-116 (H1N1) B/johannesburg/5/99
2003	A/Moscow/10/99 (H3N2) A/New Caledonia/20/99 (H1N1) - like B/Hong Kong/330/2001 - like
2004	A/New Caledonia/20/99 (H1N1) - like A/Fujian/411/2002 9H3N2) - like B/Hong Kong/330/2001 - like
2005	A/New Caledonia/20/99 (H1N1) A/Wellington/2004 (H3N2) B/Shanghai/361/2002

Source: CGPNI/DEVEP/SVS/MS

**ATTACHMENT 7**  
**Cold Chambers to Store NIP Immunobiologicals**  
**(Updated on 08/09/2005)**

Place		Capacity (m <sup>3</sup> ) <sup>1</sup>		Concluded	Number of doses <sup>2</sup>		Note
		Positive Chamber	Negative Chamber		Temperature (+)	Temperature (-)	
1	AC	-	-	No	67.011	48.686	No forecast for building the chamber Store in refrigerators.
2	AL	15,2	Does not have	2005	333.000	165.157	Chambers construction concluded
3	AP	7,2	Does not have	No	56.806	39.567	Construction underway, estimated to be launched no later than by December 2005. They use container
4	AM	-	-	No	315.163	225.074	Old chamber concluded. New Chamber Dec. 2006.
5	BA	-	-	1999	1.257.558	723.508	-
6	CE	16,8	8,8	2005	599.267	344.298	Chamber under trial and expected to be launched in Dec 2005.
7	DF	11,2	Does not have	2003	168.492	125.608	Chamber concluded and operational
8	ES	10,4	Does not have	Yes	252.759	168.417	Chamber under trial and expected to be launched in Dec 2005.
9	GO	16,0	8,0	No	509.168	333.083	Missing the bidding process for the chamber construction. Expected by July 2006. They use container
10	MA	15,2	6,4	No	438.890	362.333	Construction underway, they use container. Expected by July 2006.
11	MG	36,8	16,0	2005	1.550.644	979.810	Concluded
12	MS	10,0	Does not have	2003	212.758	115.337	Concluded
13	MT	10,7	Does not have	2005	271.478	174.947	Concluded and operational
14	PA	-	-	2001	691.728	275.059	Concluded
15	PB	-	-	1996	259.946	170.739	Concluded
15	PE	14,3	5,0	No	758.890	461.282	Construction underway for Dec /2005
16	PI	10,0	Does not have	No	233.458	147.833	Bidding process underway, expected for Jul/2006 they use container
17	PR	-	-	1997	644.616	632.230	Concluded

18	RJ	-	-	No	1.007.448	532.200	Conclusion in dez/2006, use small chamber
19	RN	7,9	Does not have	No	200.529	127.292	Construction underway Conclusion in Dez/2006
20	RO	-	-	No	166.791	104.016	Conclusion in Dez/2006, they use container
21	RR	6,5	Does not have	No	97.166	78.268	Construction underway Conclusion in jul/2006
22	RS	-	-	No	687.351	466.813	Const. for July 2006, use small chamber
23	SC	16,4	7,1	No	269.037	273.782	Bidding process underway, they use container Conclusion in jul/2006
24	SE	8,6	Does not have	2003	159.372	109.954	Concluded
25	SP municipality	-	-	No	-	-	Construction underway for Jul 2006
26	SP - state	23,6	9,3	2003	2.842.904	1.705.570	Concluded
27	TO	-	-	2001	137.802	115.643	Concluded

(1) In the states where the chamber volume is not reported, it means that there is no capacity study available by the MoH or the State built the chamber for its own sake.

(2) Number of doses of immunobiologicals distributed to the respective states during 2004.

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(2) Number of doses of immunobiologicals distributed to the respective states during 2004.

TOTAL	87	147	80	54	80	13	14	22	31
TOTAL (R\$)					R\$1,401,840.00	R\$227,800.00	R\$247,233.00	R\$388,607.00	R\$536,543.00
TOTAL (R\$)									
Source:									
Average unit price of the equipment: R\$ 17.523,00									
Average unit price of the equipment: R\$ 17.523,01									
Average value for training (2 trainees/state									
1.	Add values								
2.	Define “remote areas”								
3.	Highlight the need for refrigerators in these areas								
4.	Inform when it is an Indigenous area								
5.	Add values for training in photovoltaic refrigeration								
6.	Add values for publishing the GFV maintenance manual								
7.	Add population data (age group, Indigenous and Non-Indigenous)								
8.	Inform source of resources								
9.	Inform distances from the locality to the capital								

For the purposes of vaccination actions, “remote areas” are understood as those where at least one of the following realities can be observed:

1. Displacement to these areas is not possible by highways or other ground means and is necessary to use vessels or walk long ways;
2. Displacement is possible only by air;
3. In the same state, the displacement to these areas takes, on average, 7 hours or more.

The selection of these areas have also taken into consideration the communication difficulty, additionally to the fact that, for these sites, there is no forecast for conventional electric power supply in the forthcoming 4 (four) years.

### **ADVERSE EVENTS POST VACCINE AGAINST INFLUENZA (EPIDEMIC STRAIN)**

Local events	Local pain Erythema Induration	1 – 2 days after vaccination for 48 hours	10 – 64% dos Vaccinated individual	Notify investigate Hot abscess and very extensive local reactions with movement limitations. Administer analgesic, if necessary	No counter indication subsequent doses. Serious local events should be assessed
Systemic events	Fever. Myalgias. Cephalea. Light flu-like symptoms	6-12 hours after the vaccination for 48 hours	-	Symptomatic treatment. Remove diagnosis differentials	There is no formal counter indication subsequent doses
Anaphylactic reactions	Urticaria, sibilus, Laryngospasm, Lips edema, arterial hypotension and chock	Less than 2 hours after the vaccination	-	Fast and adequate treatment (see EAPV Manual)	Formal counter indication for subsequent doses
Guillain- Barré's Syndrome (SGB)	Inflammatory Poliradiculoneuritis with demyelination, lesion, paresthesia and ascending motor deficit of variable intensity	7 – 21 days to 6 weeks after the vaccination	-	Notify and investigate. Specialized follow-up	Assess risk- benefit of the revaccination

Source: CGPNI/DEVEP/SVS/MS

## **ATTACHMENT 8**

### **Antiviral Drugs to Prevent and Treat the Influenza**

Two classes of drugs, the inhibitors of M2 ion channels (State Sanitary Surveillance Directorate and rimantadine) and the inhibitors of neuraminidase (zanamivir and oseltamivir) are currently available for the prevention and treatment of influenza. The inhibitors of the M2 ion channel work by inhibiting the activity of the M2 protein, required for releasing the viral genetic material in the cells. Such medications reduce the virus incubation and shorten the disease length in about one day if taken 48 hours since the start of the disease. However, they still fail in reducing complications or improving the results for hospitalized patients.

The intolerance or to fast development of resistance to State Sanitary Surveillance Directorate and rimantadine are the major limitations to the use of these agents. The resistance is consequence of to single mutation point in the M2 gene, which completely ends the medication connection without affecting the transmission for susceptible contacts. Its half-life is relatively long, and since the State Sanitary Surveillance Directorate depends on the renal function of excretion, it is necessary to make adjustments to the doses and supervision in the cases of renal insufficiency.

On the other hand, the Neuraminidase Inhibitors (NI), block the neuraminidase molecule (NA), indispensable for releasing the newly formed viruses from the infected cells. The neuraminidase inhibitors are active against the human influenza to (all the 9 NA molecules) and virus B as well as against the bird virus. Two drugs in this group have been approved for influenza infections: zanamivir, which is applied through aerosol and the oseltamivir, orally ingested. The plasma half-life of zanamivir is short, but it can be found in the tracheobronchial tree over 24 hours after the inhalation of to single dose. It must be carefully used by patients with respiratory problems (asthma or Chronic Obstructive Pulmonary Disease) because of the possibility of bronchial spasms, to serious but not frequent side effect. The Oseltamivir, on the other hand, requires for the reducing doses for patients with low clearance of creatinine) (<30 mL/min). Gastro-intestinal intolerance (lasting less than one day) occurs in 5 to 15% of the patients treated with oseltamivir but rarely (<2%) causes the interruption on the medication use.

The neuraminidase inhibitors reduce the disease length in approximately one day, when used in up to 48h from the start of the disease. Although there are no studies evidencing improvements after hospitalization or reduced mortality rates after the treatment with NI for patients with influenza, there was to drop in the use of anti-biotic for respiratory conditions and reduced occurrence of secondary problems such as bronchitis clinically diagnosed and sinusitis. The neuraminidase inhibitors were recently approved for clinical use and, therefore, they still lack deeper results to confirm the safety and effect in the prevention and treatment of influenza in high-risk individuals.

### **Prophylaxis Protocol and Treatment with Antiviral Drugs**

The indications for the use of antiviral drugs in the prophylaxis and treatment of influenza are:

- a) Amantadine
  - Prophylaxis: Prevention against respiratory infections caused by the Influenza to virus;
  - Treatment: Treatment of respiratory infections caused by influenza A;

b) Zanamivir:

- Prophylaxis: it is not recommended for prophylaxis
- Treatment: acute and non-complicated diseases caused by the influenza virus in patients of more than 12 years old who present the symptoms for no longer than 2 days;

c) Oseltamivir

- Prophylaxis: in adults and adolescents of more than 13 years old. The safety and efficiency of oseltamivir for prophylaxis in pediatric patients below 13 years old have not been proved;
- Treatment: of acute diseases non-complicated caused by the influenza infection in adults who have reported the symptoms for no longer than 2 days.

Amantadine acts on the prevention when used as prophylaxis for to period of 6 weeks. When used for treatment, the medication does not interfere in the development of antibodies for protection. The resistance to the drug is induced with amantadine, when it is used for the prophylaxis and treatment concurrent in crisis. Some special issues should be taken into consideration when using amantadine in Prophylaxis, mainly for longer periods (6 weeks was the longest period formally studied in controlled attempts). The issues include the need for individual prescriptions for the use of amantadine due to its toxic level, therapeutic rates and dependence on the renal functioning for elimination. It is necessary to monitor the side effects and consider the emergence of relatively high risk of viruses resistant to the medication, by adjusting the administration when the prophylaxis fails and the treatment must be started.

Neuraminidase inhibitors have proved to be efficient for prophylaxis post-exposure and for the treatment of influenza infections. It was proved that the resistance to zanamivir and oseltamivir occurs in normal carriers. The functional groups of two Neuraminidase inhibitors have some differences in their connection place, mutants resistant to medication may be susceptible to the other.

### Recommended Doses \*

MEDICATION	PROPHYLAXIS	TREATMENT
Amantadine	Children: 1-9 years	Children: 1-9 years
	old, according to the weight <sup>a</sup>	old, according to the weight <sup>a</sup>
Zanamivir	Not approved	Children: 7 years old, 10 mg/2x/day, 5 days <sup>b</sup>
		Adults: 10mg/2x/day , 5 days <sup>b</sup>
Oseltamivir	Adults and adolescents with more than 13 years old	Children: 1 year old, according to the weight <sup>c</sup>
		Adults: 75 mg/2x/day, 5 days

a. For children of 1-9 years old the following doses of amantadine are recommended: 5.0 mg/kg to day, up to the maximum of 150mg/a day. In two doses divided. For children (10 years old weighting > 40 kg, the recommended doses are 200mg/day in two doses. For prophylaxis of up to 6 weeks, the doses shall be reduced and monitored for individuals with the fever (100mg/day) or reporting renal dysfunction.

b. Zanamivir is orally inhaled: therefore, children of 5 years or less and older adults may need assistance for using the Diskhaler supplied by the producer.

c. The use of oral suspension oseltamivir is recommended for pediatric patients. In Brazil there is no syrup.

## Amantadine Dose

– Patients with no Renal Damage

Age	Dose
1-9 years old	5 mg/kg 1x/day or 2x/day , not to exceed 150 mg
10- 64 years old	200 mg 1x/day or divided into 2 doses
65 years old or older	100 mg 1x/day

– Patients with Renal Damage

Clearance of Creatinine ml/min/1.73m <sup>2</sup>	10 to 64 years old	> or = 65 years old
80 ml/min	100 mg 2x/day	100 mg 2x/day
60-79 ml/min	Alternate doses of 100 mg and 200 mg	Alternate doses of 50 mg and 100 mg
40-59 ml/min	100 mg 1x/day	100 mg every 2 days
30-39 ml/min	200 mg 2x/week	100 mg 2x/week
20-29 ml/min	100 mg 3x/week	50 mg 3x/week
10-19 ml/min	Alternate weekly doses of 100 mg and 200 mg	Alternate weekly doses of 50 mg and 100 mg

## Dose of Oseltamivir

– Doses of Oseltamivir in children

Weight/kg	Recommended doses for 5 days
15kg	30 mg 2x/day
15 to 23 kg	45 mg 2x/day
23 to 40 kg	60 mg 2x/day
40kg	75 mg 2x/day

The doses are to be adjusted for patients with clearance of creatinine < 30mL/min.



## Side Effects and Adverse Reactions

EFFECTS	AMANTADINE*	ZANAMIVIR**	OSELTAMIVIR
Gastrointestinal	Vomit Nausea Anorexia	-----	Nausea Vomit
Central Nervous System	nervousness Anxiety Insomnia Delirium Hallucinations	-----	-----
Cardiovascular	Arrhythmia (in high doses)	-----	-----
Respiratory	-----	Bronchospasm Subjacent exacerbation of chronic respiratory disease	-----

\* Typically, the side effects are light and tend to decrease or disappear one week later, with the use of the medication. More serious effects have been observed, however, only when associated to high concentration of plasma in the medication. Toxic levels were more frequently observed individuals with renal insufficiency, fever, older patients, or under high doses of the medication.

\*\* Zanamivir is not recommended for individuals with asthma or chronic diseases of pulmonary obstructions; however, if the benefits are greater than the risks, the medication shall be carefully used under **supervision and monitoring**.

## Drugs Interactions

There are limited pieces of clinical information about the drugs interactions recommending careful observation when the drugs are administered concurrently, mainly those medications that affect the nervous system, antihistaminic or medications that may come to interfere with the kidneys excretion. The directions and information on the medicines package shall be consulted.

ChemioProphylaxis cannot replace vaccination; however, it is believed that the vaccinations will not be available (or just in short quantities) during the first months of a pandemic. Moreover, not all the patients can be vaccinated and some individuals may come to need supplementary protection until his/her antibodies reach a given protection level or because their immunological systems are defective, Since the pandemic would be a novelty for the population, the second dose of the vaccine would be necessary before the protective immunity is developed. Therefore, to protective prophylaxis it would take up to 6 weeks: 4 weeks after the first does and 2 after the second one.

During a pandemic, it is expected to have a limited supply of medications available. Therefore, the priorities for using such agents shall be established. The epidemiological surveillance shall identify and establish these priorities.

## **ATTACHMENT 9**

### **Anti-biotic Drugs for Treatment of Secondary Infections to the Influenza**

Some secondary infections inherent to the infection by influenza are common, among which the bacterial pneumonia, sinusitis and otitis. The bacterial pneumonia is the most typical secondary infection and usually employs anti-microbial therapy to fight it. Acute sinusitis is another secondary bacterial infection, but the anti-microbial are not recommended for these cases, except for cases of severe symptoms. Otitis media, another potential bacterial infection, is not common among adults, but very common among children.

The diagnosis of a secondary bacterial pneumonia shall be considered upon: worsened clinical conditions after a period of improved following the initial stage of influenza, mainly in the event of a new stage of purulent (?) or dyspnea and radiographic consolidation.

Purulent secretion without the radiographic consolidation is not an indication for the use of anti-microbial therapy, except if the patient has a pre-existing chronic pulmonary disease. However, the expectoration of purulent secretion with a normal chest X-Ray, concomitant to or soon after the influenza starts (up to 14 days) suggests the existence of bacterial bronchitis. If it is severe or occurs in an individual vulnerable to super-infection, the use of anti-biotic should be taken into consideration.

In any infection of the upper respiratory system, runny nose and inflammation are common. In some cases, in the event of severe symptoms persisting for more than 10-14 days, a bacterial sinusitis may be present.

The acute sinusitis is clinically presented with purulent nasal mucus, pain in the maxillary tooth on the face (mainly unilateral), these symptoms are worsened after the initial bettering from the influenza. In children, the suspect of sinusitis of 10 days to 2 weeks of symptom is likely to be treated, what may not occur with adults. Bacterial acute sinusitis does not require for treatment with anti-biotic in case of light or moderate symptoms.

Most of the patients with clinical diagnosis of sinusitis get better with no anti-biotic treatment and, therefore, the treatment will be made with appropriate doses of analgesics, anti-pyretic and nasal decongestant. Only the patients with severe or persistent symptoms and with clinical diagnosis specific for bacterial sinusitis shall be treated with anti-microbial. Anti-biotic drugs of limited spectrum are reasonable first-line agents for these patients.

The issues to be considered when promoting an anti-microbial therapy in an influenza pandemic:

- The availability of anti-microbial treatment during a pandemic could be limited because of the increased demand. The influenza infection, per se, with no secondary bacterial complications, shall not be treated with antimicrobial drugs;
- A broad variety of antimicrobial agents shall be efficient for the treatment of secondary bacterial pneumonia. As general rule, it is not advisable to treat all individuals with the same anti-biotic drug, since it could promote resistance to the anti-microbial drugs and limit the medication efficacy. Several anti-microbial drugs are efficient, as listed in **Table 1**. The use

of anti-microbial drugs for the empirical treatment shall be regularly reviewed and updated, considering the availability of new drugs and the evolution of the bacterial resistance among the respiratory pathogens;

- Staphylococcus aureus is an isolate pathogen frequent in secondary bacterial pneumonia and the initial anti-microbial therapy should include the coverage for the Staphylococcus aureus susceptible to oxaciline. Other bacteria include Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, and Streptococcus of group A. The anti-microbial of broader spectrum for resistant organisms shall be considered under given circumstances: patients who had already presented infection by a resistant organism; patients who have failed or repeated the initial anti-microbial therapy; and patients with severe clinical conditions, including respiratory failures or hemodynamic instability;
- The anti-microbial resistance should be considered in an anti-microbial selection. Brazil still lacks accurate data on microbial resistance. The prevalence of anti-microbial resistance in typical respiratory pathogens shall be monitored in the pre-endemic period and during a pandemic among patients with bacterial pneumonia. The information should be provided to the physicians or practitioners in due time.
- For hospitalized adult patients with diagnosis of bacterial pneumonia, culture and sensitiveness assays should be made whenever possible. Once the culture results are available, usually in 48-72 hours, the anti-microbial therapy should be reassessed based on the results. Species of outpatient mucus are not recommended for routine cultures; such cultures should be made among patients who have recently taken anti-microbial drugs or, if the clinical response to the initial anti-microbial therapy is adequate;
- Outpatient may be treated with oral therapy. Hospitalized patients will undergo parental therapy, but the oral therapy may be considered for selected cases. The parental therapy shall be converted into oral therapy as soon as the patient is stabilized. The selection of an anti-microbial agent shall be based on the secretion or hemoculture and the sensitivity results, the patient's tolerance, local prevalence of anti-microbial resistance and availability.

**Table 1. Empirical Anti-Microbial Therapy for the Treatment of Acute Secondary Bacterial Pneumonia ( Adults  $\geq$  18 Years old)**

Medication	Administration was	1st Choice	In case of resistance	Other choices
2 <sup>nd</sup> Generation Cephalosporin	Oral and Parenteral	X (Oral)	---	X (Parenteral)
Clarithromicine*	Oral	X	---	---
Azitromicina)*	Oral	X	---	---
Eritromicina*	Oral	X	---	---
Doxiciclina	Oral	X	---	---
Trimetoprima/sulfametoxazol	Oral	X	---	---
Amoxicilina/ clavulanic acid	Oral and Parenteral	---	X	---
Levofloxacin	Oral and Parenteral	---	X	X (Parenteral)
Moxifloxacin	Oral and Parenteral	---	X	---
Gatifloxacin	Oral and Parenteral	---	X	---
3 <sup>rd</sup> Generation Cephalosporin	Oral and Parenteral	---	---	X

Piperacillin/tazobactam	Parenteral	---	---	X
Gatifloxacin	Oral e Parenteral	---	---	X
Imipenem	Parenteral	---	---	X
Meropenem	Parenteral	---	---	X

\* Macrolides should only be used as a first line agent when the presence of bacteria is unlikely.

**Table 2. Anti-microbial for the Treatment of Secondary Bacterial Pneumonia in Patients whose Infecting Organisms and Susceptibility are known through the Sputum or Blood Culture ( ≥ 18 years old).**

Microorganism	Specificity	Anti-microbial
Streptococcus pneumoniae	Sensitive to penicillin	Penicillin G, amoxicilina, eritromicina*, claritromicina*, azitromicina*, doxiciclina*
	Resistant to penicillin	Amoxicilina (high dose), levofloxacin, Gatifloxacin, Moxifloxacin, 3 <sup>rd</sup> Generation Cephalosporin
Haemophilus influenzae	Negative Beta lactamase	Amoxicilina, ampicillin (IV), cefuroxime, claritromicina, azitromicina
	Positive Beta lactamase	TMP/SMX, 2 <sup>nd</sup> Generation Cephalosporin, 3 <sup>rd</sup> Generation Cephalosporin, claritromicina*, azitromicina*, Amoxicilina/ clavulanic acid, ciprofloxacin, levofloxacin, Gatifloxacin, Moxifloxacin
Staphylococcus aureus	Sensitive to methicillin	Cloxacilina, TMP/SMX, 1 <sup>st</sup> Generation Cephalosporin, claritromicina*, azitromicina*
	Resistant to methicillin	Vancomicina, linezolid

Note: when the organisms are isolate by cultures, the final anti-biotic therapy shall be oriented by the sensitivity assay and by the availability of specific anti-biotic drugs.

\* Macrolides should only be used if the bacteremia is absent.

### Treatment of Bacterial Pneumonia in Children

When the pneumonia is diagnosed (or there is a strong suspect), the anti-biotic therapy should be promptly started. Whenever possible, the saliva Gram (mucus?) or tracheal aspirated should be made. Otherwise, an empirical treatment is to be started (based on the frequency of pathogens for the different age groups and in the agents most typically found in the community). Children with light diseases may be treated at home: however, the hospitalization is recommended for extremely young children (first year of life), children with severe diseases and/or who present severe pulmonary disease and also for children who may not receive the proper care at home.

**Table 3. Empiric Anti-microbial Therapy for the Treatment of Acute Secondary Bacterial Pneumonia for Children**

Age	Outpatient (Oral)	Hospitalized Patients	Hospitalized Patients with Signs of Sepsis of Pleural Infiltrated
3 weeks to 3 months	No fever: eritromicina or azitromicina	No fever: Eritromicina* IV fever: add cephataxime	cephotaxime IV
4 months to 4 years	Amoxicilina	Ampicillin IV	Cephataxime IV ou Cefuroxima IV ou Ampicillin IV
5 years to 15 years	Eritromicina or Claritromicina or Azitromicina or Doxiciclina (> 8 years)	Eritromicina* IV or Azitromicina* IV or Doxiciclina IV (>8 years)	Cephataxime IV or Cefuroxima IV Consider adding Azitromicina IV

\* Macrolides should only be used if the bacteremia is unlikely.

**Table 4. Anti-microbial drugs to Treat the Secondary Bacterial Pneumonia in Children where the Infecting Organism and Susceptibility are known through Sputum or Blood Culture ( $\leq 18$  years)**

Microorganism	Specificity	Anti-microbial
Streptococcus pneumoniae	Sensitive to penicillin	Penicillin G(IV,IM), Penicillin V(Oral) Claritromicina*, Azitromicina*, TMP/SMX
	Resistant to penicillin	3rd Generation Cephalosporin, Vancomicina
Haemophilus influenzae	Negative Beta lactamase	Amoxicilina, Ampicillin (IV), Claritromicina*, Azitromicina*
	Positive Beta lactamase	2nd generation Cephalosporin, 3rd generation Cephalosporin, Amoxicilina/ clavulanic acid, Claritromicina*, Azitromicina* e TMP/SMX
Staphylococcus aureus	Sensitive to methicillin	Cloxacilina, 1st generation Cephalosporin
	Resistant to methicillin	Vancomicina, Linezolid (uses Clindamicina or TMP/SMX if sensitive)

Note: when the organisms are isolate by cultures, the final anti-biotic therapy shall be oriented by the sensitivity assay and by the availability of specific anti-biotic drugs.

\* Macrolides should only be used if the bacteremia is absent.

The medication elected for the pneumonia caused by the *S. pneumoniae* is the Penicillin G, Cefotaxime or Cephataxime shall be used if the isolate is resistant to Penicillin and the vancomicina is to be used for organisms resistant to both.

## **ATTACHMENT 10**

### **Requirements for Reference Hospitals in Serving Patients with Suspicion of Infection by New Influenza Strain**

During the pandemic alert period, the health system should be prepared to receive suspect cases of influenza, possibly patients with respiratory symptoms compatible with influenza coming from affected countries. These hospitals should be previously defined according to their structure, organization and geographical location. The listing of these hospitals should be available in all health services, seaports and airports and be known by general population, so that suspect cases may be forwarded quickly and adequately to the reference hospitals.

These hospitals should meet the pre-requisites disclosed below to assure quality in assistance and in capacity of case isolation:

- 1) Commission of Hospital Infection Control present and acting according to requirements of Ordinance 2616m dated May 12<sup>th</sup>, 1998, which provides on Hospital Infection Control. (available at <http://e-legis.bvs.br/leisref/public/home.php>)
- 2) Tertiary hospital.
- 3) Reference infectologist doctor.
- 4) Reference pulmonologist doctor.
- 5) Respiratory isolation rooms with negative pressure, according to specifications contained:
  - in RDC 50, dated February 21<sup>st</sup>, 2002, which provides on Technical Regulation for planning, programming, elaborating and evaluating physical projects of health assistance establishments (available at <http://e-legis.bvs.br/leisref/public/home.php>)
  - in RDC 189, dated July 18<sup>th</sup>, 2003, which provides on regulation of analysis, evaluation and approval procedures of physical projects of health establishments in the National System of Sanitary Surveillance, changes the Technical Regulation approved by RDC 50, dated February 21<sup>st</sup>, 2002, and establishes further provisions. (available at <http://e-legis.bvs.br/leisref/public/home.php>)
- 6) ICU beds with respiratory isolation according to specifications of item 5.
- 7) Employees' work shift for serving patients in influenza isolation
- 8) Microbiology laboratory, with technicians qualified to collect and prepare transportation of clinical samples for influenza diagnose, according to:
  - attachment 3 in this Plan.
  - Clinical Microbiology Manual for Infection Control in Health Services, available at <http://www.anvisa.gov.br/servicosaude/manuais/microbiologia.htm>.
- 9) Central of Sterilized Material, according to specifications contained:
  - in RDC 50, dated February 21<sup>st</sup>, 2002, which provides on Technical Regulation for planning, programming, elaborating and evaluating physical projects of health assistance establishments (available at <http://e-legis.bvs.br/leisref/public/home.php>)
- 10) Laundry according to specifications contained:
  - in RDC 50, dated February 21<sup>st</sup>, 2002, which provides on Technical Regulation for planning, programming, elaborating and evaluating physical projects of health assistance establishments (available at <http://e-legis.bvs.br/leisref/public/home.php>)

11) Hospital pharmacy, with responsible technical professional, and according to specifications contained:

- in Decree no. 79094, dated January 5<sup>th</sup>, 1977, which regulates Law no. 6.360, dated September 23<sup>rd</sup>, 1976, which subjects to a sanitary surveillance system the medications, pharmaceutical raw materials, drugs, related articles, cosmetics, hygiene products, cleanser, and others. (available at <http://e-legis.bvs.br/leisref/public/home.php>)

12) Planning of IPE supply

## **ATTACHMENT 11**

### **Structure of the National System of Sanitary Surveillance**

The National System of Sanitary Surveillance – SNVS – is comprised of the National Agency for Sanitary Surveillance (ANVISA), the National Council of State Health Secretaries (CONASS), the National Council of Municipal Health Secretaries (CONASEMS), the State, Federal District and Municipal Sanitary Surveillance Centers (VISAS), the Central Public Health Laboratories (LACENS), the National Institute for Quality Control in Health (INCQS), the Oswaldo Cruz Foundation (FIOCRUZ), and the State, District and Municipal Health Councils, in regard to sanitary surveillance actions.

The National Health Surveillance Agency was established by Law 9.782, of January 26, 1999. The Agency is designated an autonomous agency operating under a special regime. This means that ANVISA is an independently administered, financially-autonomous regulatory agency, with security of tenure for its directors during the period of their mandates. The Agency is managed by a Collegiate Board of Directors, comprised of five members. Within the structure of Federal Public Administration, the Agency is linked to the Ministry of Health, under a Management Contract.

The institutional purpose of the agency is to foster protection of the health of the population by exercising sanitary control over production and marketing of products and services subject to sanitary surveillance. The latter embraces premises and manufacturing processes, as well as the range of inputs and technologies concerned with the same. In addition, the Agency exercises control over ports, airports and borders and also liaises with the Brazilian Ministry of Foreign Affairs and foreign institutions over matters concerning international aspects of sanitary surveillance.

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## **ATTACHMENT 12**

### **Reference Hospitals - Pandemic Warning Period**

The list of reference hospitals for suspected cases during the pandemic warning period will be concluded after inspection.

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## Recommended Texts

Each chapter of this document contains the specific bibliography, however we would recommend reading:

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