GOVERNMENT OF THE REPUBLIC OF CROATIA

NATIONAL PANDEMIC INFLUENZA PREPAREDNESS PLAN

Zagreb, October 2005

Acronyms:

GRC – government of the Republic of Croatia
MHCQ – Ministry of Health of the Republic of Croatia Crisis Headquarters
PMCD-MHCQ – Preventive Medical Care Department, Ministry of Health of the Republic of Croatia Crisis Headquarters
CHQ – County Health Headquarters
CNIPH - Croatian National Institute of Public Health
CPHI – County (and Zagreb City's) public health institute
WHO – World Health Organization
NCIP – National Committee on Intrapandemic Planning

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Introduction

During the interpandemic interval, the viruses circulating in the population are related to the viruses from the previous pandemic. Every two-three years, a selection takes places among the strains that are sufficiently different from the virus to which the population has high collective immunity, and are thus capable of causing an epidemic among the population. Such changes in the dominant virus are termed "antigenic drift". Typical influenza outbreaks will cause an increase in the incidence of pneumonia, reflecting in an increased number of hospitalisations and higher mortality. The elderly, individuals affected by chronic diseases and sucklings are most prone to developing the complications of influenza.

Upon a virus with very different subtype of the basic surface antigen, a haemagglutinin against which the population has not previously acquired any antibodies, establishing in circulation a pandemic will arise. Such change in the circulating virus is called "antigenic shift". It was believed that pandemics occur at regular intervals, a view that is now obsolete. On the establishment of an effective targeted virologic monitoring system, came the realisation that newly generated influenza A subtypes do not necessarily lead to a pandemic. A case in point was the isolation in May 1997 of the influenza A (H5N1) virus in Hong Kong from the clinical specimens of a child who had died of influenza. This virus is related to the avian subtype, but at the time, this subtype did not cause any other human cases. Nevertheless, in November 1997 a cluster of 17 cases diseased with the influenza caused by a related virus were detected in Hong Kong. They presented severe clinical pictures; five of the affected died. Simultaneously, an epizootic infection with the same influenza virus, A(H5N1) was discovered among the fowl in Hong Kong. Fortunately, there occurred no new human cases after the mass slaughter of fowl there. Therefore, the virus was insufficiently adapted to man to instigate an effective human-human transmission.

Based on this and similar experiences, it was realised that the ability of the virus to spread among humans is determined by some properties in addition to its antigenic subtype.

The interval between the discovery of a new viral subtype and a fully blown pandemic may be too short for developing a vaccine. Irrespective of the impossibility to purchase a vaccine in time to prevent the pandemic, any activity in preparation for the pandemic is useful. Possibly, (mostly seasonally conditioned) pauses will occur during the global spread of the virus, affording an opportunity for the accelerated application of preventive measures (assuming these have been readied beforehand).

For instance, in 1918 Belgium suffered three pandemic waves interrupted with 3-month pauses. During the 1968/69 Hong Kong influenza pandemic, 18 months had passed between the isolation of the pandemic strain in Hong Kong and the occurrence of a fully expressed pandemic in Europe.
There are three theories on pandemic virus emergence (i) theory of genetic recombination between human and animal influenza viruses, (ii) theory of direct animal-human transmission of the virus and vice versa, (iii) theory about the emergence of new viruses,

respectively introduction of formerly existent viruses into human population from an unrecognised reservoir. The recombination theory is most acceptable regarding the A(H3N2) virus that has caused the 1968/69 pandemic.

The direct transmission theory is the most plausible explanation for the appearance of the A(H1N1) virus, which has caused the 1918 pandemic (so-called Spanish influenza). As to the third theory, it is the most likely explanation for the re-emergence of the A(H1N1) virus, the agent of the so-called Russian pandemic of 1977, which was almost identical to the virus isolated in 1950. It is not known where and how this virus had survived those 27 years.

Because of the fear of a potential pandemic outbreak, the emergence of a new influenza virus subtype affecting a mere handful of infected people might put an enormous strain on the health system and government even in the absence of the pandemic.

Stages of the pandemic

To deal more effectively with "false alarms", which are a consequence of improved virologic surveillance over influenza virus trends, definitions have been provided for the stages in a pandemic to facilitate the preparedness.

Because of the great likelihood that it might not be feasible to produce the vaccine in sufficient amounts at the outbreak of the pandemic, WHO requires each member state to draw up its own National Influenza Pandemic Preparedness Plan. Other reasons are the probable shortage of drugs to treat influenza and its complications, and the burden on health service definitely exceeding the one existing in any other circumstances.

Further, the role of WHO in global preparedness has also been defined. Its activities are divided into stages of the pandemic and into interpandemic period. National plans must equally take account of the stages given below:

- Interpandemic period
  Stage 1
  Stage 2
- Pandemic emergence period
  Stage 3
  Stage 4
  Stage 5
- Pandemic period
  Stage 6 (classed into four levels: one's own country being unaffected, one's own country being affected, end of the epidemic, and other and subsequent epidemic waves)
- Post-pandemic period.

Member state obligations

The obligations of Member states include:

1. Establishing a National Committee on Intrapandemic Planning (NCIP). It should have few standing members who would enable the continuity of its operation. If necessary, the Committee could engage additional experts in the case of need for their expertise.

- Basing itself on the health organisation experience in crises (primarily during Croatian War of Defence), the Ministry of Health and Social Welfare has established a Ministry of Health Crisis Headquarters (MHCQ) by health minister's decree. Structurally, the MHCQ has been shaped into a co-ordinating body to run the local self-government units. For this purpose, it has set up health headquarters in all counties (CHQs). The MHCQ is made up of departments, one of these being in charge of preventive medical care (PMCD), precisely to run epidemic control activities. Organisationally, the MHCQ is a government administrative body for managing crises and catastrophes; its acts as a link between the existing governmental bodies, local self-government and technical organisations with the view to meeting the challenges.

- Because as an administrative body, PMCD uses Croatian National Institute of Public Health as Croatia's central public health body nationally, and county public health institutes (CPHIs) on the level of the local self-government, it constitutes a primary link both with governmental administrative authorities and local self-government bodies, as well as reaching out to other technical health organisations.

- The PMCD has fewer standing members who follow up the activities regularly, and they can at any time engage other experts as needed and according to the nature of the task.

- The PMCD MHCQ has the capability to take over completely the role of NCIP.

2. Ensuring effective management process - by defining the chain of command for an emergency.

- In order to ensure the effectiveness of the management process, Croatian government should pass a National Influenza Preparedness Plan (further herein: the National Plan). Assignment of activities and nomination of carriers unfold within the National Plan. By enacting the National Plan, relevant sectorial ministries take up within their respective purviews the responsibility to carry out the activities fixed by the National Plan. Hence, the Ministry of Health undertook to make the MHCQ operational.

- At the county level, it is essential to activate the CHQs whose purpose it is to assure the realisation of the NCIP recommendations. Given that the recommendations to be followed pertain to different segments of societal action,

the CHQ members should, like the NCIP's, be written by county-level experts. At a minimum, these should be CPHI Epidemiology Service heads (further herein: CPHI), county government officials, a prominent clinician from some general hospital in the county, or a veterinarian or sanitary inspector from the county.

3. Making an immunisation strategy decision. One of NCIP's first responsibilities is to recommend the size of the vaccination campaign in the case of a pandemic.

- Going on the past experience, it is known that people aged 65+ years and individuals affected by chronic diseases will be at high risk of influenza complications or death
- Until the emergence of a new influenza virus subtype with a pandemic potential, no reliable prediction can be made regarding what other population categories could constitute risk groups for influenza pandemic complications and death
- Health workers whose work would be particularly important in the course of a pandemic should be also be vaccinated to prevent a possible shortage of skilled staff due to high morbidity in the circumstances of increased demand for health workers
- Therefore, vaccination is recommended primarily to:
- People aged 65+ years
- Chronic patients
- Groups that would exhibit increased exposure to the risk in the pandemic situation.

Health workers are essential personnel in the case of pandemic. Therefore, depending on the size of vaccine supply and this influenza (as also of common influenza), health workers should come next to the priority group in receiving the vaccine. Services vital to the functioning of the state should also be covered by the vaccination. It would be optimal for vaccination continuation to cover the whole population as well.

4. Planning a comprehensive influenza control strategy for the case of pandemic. NCIP should compile the action plan in the case of pandemic.

5. Strengthening the epidemiologic and virologic (laboratory) influenza monitoring system

- Although the epidemiologic influenza monitoring system is a part of the information system that monitors communicable diseases, it has some specific characteristics.
- They are:
- In collaboration with all CPHIs, Zagreb Institute of Public Health, Dr Fran Mihaljevic Infectious Disease Clinic, Childhood Disease Clinic, paediatricians and family doctors affiliated to Family Medicine Service, CNIPH's Infectious Disease Epidemiology Service is to organise sample collection for serologic and microbiologic diagnoses. This step must be taken as the first individual clinical

picture-based notifications of influenza cases start coming in, and when a clustering of the clinical syndrome of influenza occurs. Any action that the Service takes it must promptly report to PCMD MHCQ.

- Upon influenza being confirmed (by means of serology, antigen identification or virus isolation), CNIPH's Infectious Disease Epidemiology Service should inform the PCMD MHCQ by circular letter of the onset of influenza (the latter forwards the letter to CPHIs) and of the transition to weekly, i.e., comprehensive reporting on influenza.
- Influenza case parameters reported include age group, local hygiene-epidemiology unit and epidemiological week. The reasons for using this type of reporting are (a) the impossibility of processing the individual case notification total that will be seen in the influenza epidemic, (b) maintaining the possibility of obtaining epidemiologically relevant data.

- It is essential to maintain and secure the smooth operation of the virologic diagnostics of influenza laboratory at CNIPH. For this, it is imperative to ensure funds for supplemental equipping of the laboratory and, if necessary, strengthen the laboratory in terms of skilled staff. Due to the work involving exceptionally pathogenic influenza virus strains, the laboratory must undergo adaptation to meet the high protection level requirements of BSL-III/IV.

- Public health laboratories, epidemiology services of county public health institutes and Epidemiology Service of the Zagreb Institute of Public Health should acquire a supply of transporting culture media for samples from which influenza virus isolations are made, thus making quick sample transportation to CNIPH feasible.

- Vaccinators should actively monitor the occurrence of influenza among vaccinees and microbiologically process to prove/rule out any suspicion of increased number of cases, as well as to isolate and type the influenza virus.

6. Medical and scientific circles reaching a consensus on the effects of the influenza pandemic on the population

- A large portion of the scientific and technical public is aware of the importance of an influenza pandemic. Distributing copies of the National Preparedness Plan for Influenza Pandemic (further herein: National Plan) to all health institutions and to the authorities responsible for activity execution will help control the pandemic.

7. Ensure a sufficiency of vaccines, drugs and the logistics

- In the interpandemic period, the Ministry of Health and Social Welfare ensures annually through Croatian Institute for Health Insurance (further herein: CIHI) the quantity of vaccine predicted to be sufficient for immunising the groups at increased risk of complications/death from influenza. This assessment is made by Croatian National Institute of Public Health's Infectious Disease Epidemiology Service

- Declaring the pandemic and its course could spur a high demand for vaccine

- NCIP will pass recommendations regarding the necessary quantity of the vaccine, depending on prevailing circumstances. If, however, the Republic of Croatia happens to be among the first countries affected by the pandemic, it would be unrealistic to expect that the vaccine could either be available in sufficient quantities or on time. In consequence, it is necessary to secure a sufficient stock of antivirals that are effective in influenza treatment and prophylaxis

- Amantadine and rimantadine are effective in both treating and providing prophylaxis for the influenza caused by influenza-A type virus. Considering that a new subtype of A will most likely cause the influenza pandemic, it is essential to make provision for a supply of these drugs in the quantity anticipated to alleviate the first wave of the pandemic. This is one of the prime tasks of the Ministry of Health and Social Welfare within the preparations against the potential pandemic. Nevertheless, these drugs have not been demonstrated to be effective against influenza virus A/H5N1

- Zanamivir and oseltamivir are also neuraminidase inhibiting antivirals, which have an effect on influenza type A and B viruses. The scope of their indications, however, is slightly narrower than those of the first two drugs are, and their use is mostly connected with children

- Rimantidine should be given preference over amantidine, since it causes fewer side-effects while being equally effective

- A sufficient supply both of antibiotics for the treatment of complications of influenza (secondary pneumonias) and of those for supportive therapy should be ensured

- Because of increased hospital capacity needs, every county must draw up a plan for increased number of inpatient admissions for complications of influenza

- Regardless of the endeavours made to mitigate the consequences in the case of pandemic, mortality will be substantially greater than the usual population mortality. In this connection, each county must envisage enlarging the capacity of its present funeral homes.

8. Preparing a political-economic framework for action

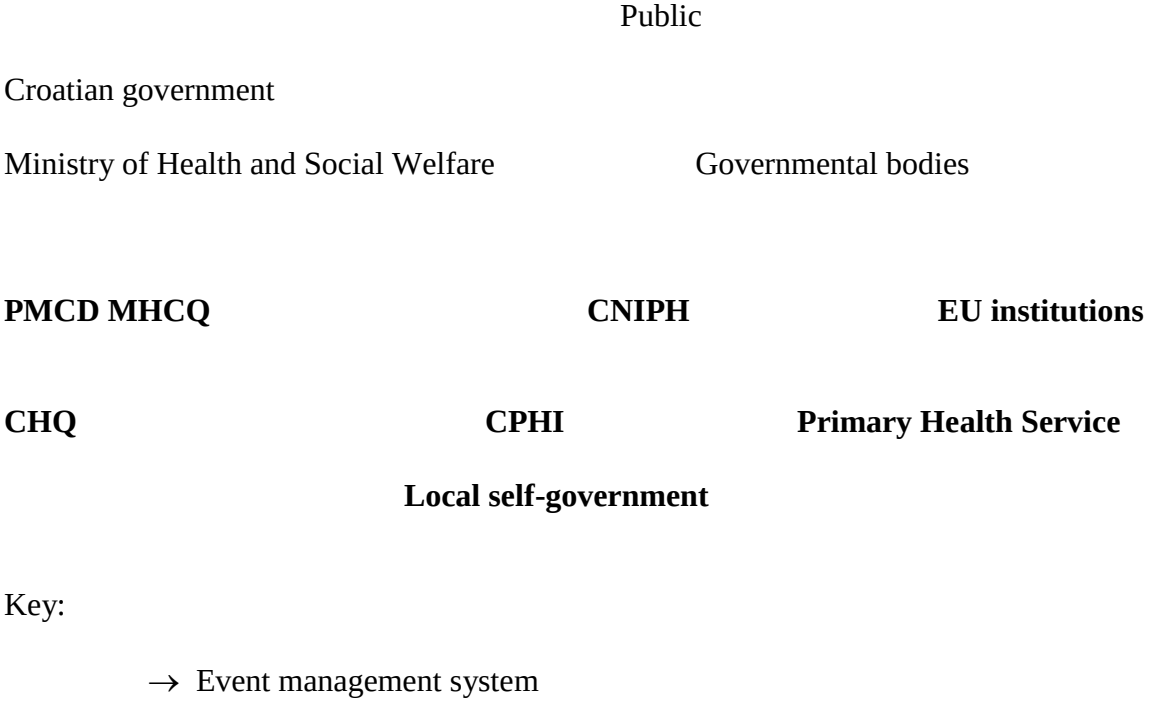
    - All ministries must be prepared for the case of pandemic and are obliged to work out within six months the National Plan-action-based protocols.

9. Assuring the flow of information. The National Plan should contain directives on the dissemination of information to health workers and the public, to the fight against disinformation and panic.

Disseminating information is MHCQ's responsibility. Any recommendation forwarded by MHCQ to the Croatian prime minister shall be published in the media in a form adapted to the public after its adoption.
It is thus essential to provide a mechanism that would enable a rapid adoption of MHCQ's recommendations. In the ideal scenario, at stage five, i.e., immediately before the pandemic is declared, the prime minister could empower the MHCQ to continue making recommendations.

10. Passing a National Plan in conformity with the current WHO recommendations, taking into account the organisation of the health care system in the Republic of Croatia.

Fig. 1 Crisis management and information system in health in the area of epidemics



ACTIVITIES PREPARATORY TO CONTROLLING AN INFLUENZA

PANDEMIC

STAGE	ACTIVITY CARRIERS	ACTIVITY
Interpandemic period: Stages 1 and 2 **Stage 1 characteristics:** An interval free of indications of a new influenza virus subtype emerging in humans. In animals, the existence of the virus subtype that has caused human disease is possible, but the risk[1] of human infection or disease is considered to be low.	CNIPH: Epidemiology Service, Reference Centre of the Ministry of Health and Social Welfare (further herein: **CNIPH-epidemiology**)	Monitor influenza trends abroad in collaboration with national collaborative centres. Monitoring and analysing influenza trends in Croatia and notifying WHO about it. Organise, do the surveillance and evaluation of the influenza vaccination campaign.
	CNIPH: Microbiology Service, National Reference Centre for Influenza (further herein: **CNIPH-virology**)	Equip the influenza serologic and virologic diagnostic laboratory. Equipping the public health laboratories and epidemiologic services of CPHIs with transportation media. Perform diagnostic activities in the course of influenza season, especially respiratory virus isolation. Collaborate with the Regional Reference Laboratory for Influenza.
Characteristic of stage 2: an interval still free of indications of the emergence of a new virus subtype in humans. Nevertheless, the animal virus subtype, circulating among animals, poses a risk[2] to humans.	County Health Headquarters (CHH)	Ensure, for pertinent public health institutes, the possibility of rapid sample transportation for viral diagnostics. Draw up a hospital capacity expansion plan to manage the patients affected by influenza complications and enlarge funeral home capacities in the case of pandemic. Make a plan for engaging more home visiting nurses to administer therapy to the patients treated at home. Monitor influenza trends in own area and keep CNIPH

		notified of these.
[1] The assessment of risk posed to humans by a subtype circulating in animals depends on several factors. They include the present knowledge of virus pathogenicity, depending on whether the virus has appeared in domestic or in wild animals only, and on whether its occurrence is enzootic or epizootic in character, on the geographic spread of virus, on information on virus genome and on other scientific knowledge.	Ministry of Health and Social Welfare (further herein: MHSW), **Croatian government.**	Create preconditions for the import of drugs, i.e., start registration procedure for antivirals.
	Ministry of Agriculture, Forestry and Water Management, Veterinary Administration (further herein: MAFWM)	Monitor influenza virus trends in fowl and pigs abroad in collaboration with international institutions.
	Primary health care physicians, special and consulting medical service physicians, and clinicians in infectology and other hospital departments (further herein: **physicians of first contact)**	Notifying MHCQ and competent epidemiology departments of individual influenza cases; later, doing so via weekly notifications and participating in sample drawing for microbiologic and serologic diagnoses. Actively monitor influenza morbidity among the vaccinated.

ACTIVITIES PREPARATORY TO CONTROLLING AN INFLUENZA PANDEMIC — Cont'd

STAGE	ACTIVITY CARRIERS	ACTIVITY
The period of increased pandemic risk – Stage 3 **Stage 3 characteristics:** though the new influenza virus subtype infects humans, either there is no interhuman transmission, or the cases of transmission to a person in close contact are rare.	**CNIPH-epidemiology**	Disseminate MHCQ's notice to have it forwarded to everyone involved in influenza control and monitoring. Continue all stage 2 activities.
	CNIPH-virology	Draw up a list of reagents and equipment, and equip the laboratory for diagnosing the newly discovered virus subtype. Check whether public health laboratories and epidemiologic services have the transportation media. Continue performing diagnostic tests and collaboration with the **Regional Reference Laboratory.** Notify MHCQ the completed activities.
	County health headquarters	Check whether all stage 2 activities for which the Office is responsible have been completed.
	MHSW, Croatian government	Procure drug stocks. Reserve the vaccine.
	MAFWM, first contact physicians	Continue stage 2 activities.

STAGE	ACTIVITY CARRIERS	ACTIVITY
Period of increased pandemic risk – Stage 4	**CNIPH-epidemiology**	Disseminate the MHCQ notice to have it forwarded to everyone involved in influenza control and monitoring. Inform the media. Continue all stage 3 activities
A stage 4 characteristic: small clusters with limited interhuman transmission. Viral spread is limited, indication that the virus has not adapted to humans well.	**County health headquarters**	Institutes whose area is more likely to be visited by travellers from a country in which the new subtype had been isolated should focus on identifying the individuals with manifest symptoms of influenza, who have arrived from an infected area, and on taking samples for virologic diagnosis (regardless of influenza season).
	CNIP-virology, MHSW, MAFWM	Continue stage 3 activities
	Physicians of first contact	Continue stage 3 activities with a focus on instant influenza syndrome cluster reporting (irrespective of influenza season).

STAGE	ACTIVITY CARRIERS	ACTIVITY
Period of increased pandemic risk – Stage 5 **A stage 5 characteristic:** bigger clusters, but without interhuman transmission, which is still localised, an indication of improved adaptation of the virus to humans but without it acquiring the pandemic potential (high contagiousness).	**MHCQ**	Convene an MHCQ session. Propose an antiviral utilisation plan. Consider vaccine procurement and utilisation possibilities, depending on availability. Write recommendations. Declare the danger of a pandemic outbreak, and organise communication with the media and the public, i.e., appoint an individual or organising body to be exclusively authorised to release reports for the media and public about the pandemic. Keep in daily contact with the WHO and other international institutions. Meet in daily sessions and regularly inform the medical profession; inform the public through the media. Develop guidelines for health workers and laboratories on patient management and infectious material handling. Set priorities for anyone involved in influenza control and monitoring. Inform the MHSW about every aspect of pandemic control planning.
	CNIPH-epidemiology	Continue stage 4 activities, and take up the responsibility for executing the MHCQ decisions pertaining to the purview of epidemiology. Organise intensified virologic and epidemiologic monitoring

		(increased number of samples). Depending on MHCQ's assessment, introduce the null reporting. Do a serologic-epidemiological survey of the population's sensitivity to the new virus.
	CNIPH-virology	Procure the newly discovered virus for the needs of serology as also the requisite reagents for virus detection. Possibly produce own diagnostic reagents to the new strain. Decide what technique is optimal for new virus identification. If necessary, acquire both supplemental equipment and staff. Revise the current guidelines on infectious material handling for laboratory staff. Ensure 24-hour laboratory availability (preparedness/on-duty shifts). Develop a serologic test for examining the population's susceptibility to the new virus.
	County Health Headquarters	Act according to the MHCQ guidelines.
	MHSW	Provide funds for the implementation of MHCQ guidelines within the health system.
	MAFWM	Ensure the implementation of MHCQ guidelines within your competence, i.e., intensify the monitoring of influenza virus circulation in fowl and pigs in Croatia.

	Physicians of first contact	Continue stage 4 activities, and notify the epidemiologic service of the occurrence of the first cases of influenza syndrome and taking part in sample collection for virologic tests.

STAGE	**ACTIVITY CARRIERS**	**ACTIVITIES**
Pandemic period – Stage 6 (Republic of Croatia still unaffected by the pandemic)	**MHCQ**	Declare the onset of the pandemic based on WHO recommendations. Intensify and accelerate the vaccination procurement procedure. Publish guidelines on the use of antivirals. Inform the public regularly.
A stage 6 characteristic: Increased and permanent virus transmission in the general population	**CNIPH-epidemiology**	Having procured the vaccine, ensure its distribution and use according to the recommendations. Intensify the monitoring of influenza virus trends and morbidity. Advise the MHCQ continuously. Carry out a seroepidemiologic investigation to establish whether the population is susceptible to the new strain.
	CNIPH-virology	Pursue stage 5 activities intensively.
	County Health Headquarters	Organise vaccination in your area in line with MHCQ guidelines and in collaboration with CNIPH.
	MHSW	Ensure the funding for the implementation of MHCQ guidelines within the health system.

	MAFWM	Ensure the implementation of MHCQ's guidelines within your purview and intensively supervise the influenza virus circulation in Croatia's fowl and pigs.
	Physicians of first contact	Continue stage 5 activities and notify the epidemiologic service of the first cases of influenza syndrome, also participating in the collection of samples for virologic tests.

STAGE	**ACTIVITY CARRIERS**	**ACTIVITIES**
Pandemic period – Stage 6 (either the Republic of Croatia or some country with which we have intensive trading relationships and exchange of people (travels and goods) is affected by the pandemic.	**CNIPH-epidemiology**	Based on expert assessment, the vaccine may be redistributed and MHCQ can be advised to purchase extra supplies of it. Supervise intensively the circulation of influenza in the population by place, age, and risk group. Collect for virologic tests the samples drawn. Reporting to WHO.
A stage 6 characteristic: Increased and permanent virus transmission in the general population	**CNIPH-virology**	Samples must undergo virologic tests for the identification of circulating strains. Test circulating strains for sensitivity to antivirals. If necessary, increase the working capacity by using the space and equipment of other corresponding laboratories.
	CHQs	Expand hospital capacities in terms of equipment, number of beds, as well as number of health workers.
	All activity carriers	Continue activities from the previous level, bringing possible modifications

		based on MHCQ recommendations.

STAGE	ACTIVITY CARRIERS	ACTIVITIES
Pandemic period – Stage 6 – The end of first pandemic wave	**MHCQ**	Declare the end of the first pandemic wave in keeping with the WHO recommendations. Continue purchasing the vaccine within the means. If necessary, modifying recommendations on the basis of CNIPH's expert opinion.
	CNIPH-epidemiology	Organise the distribution of additional doses of vaccine and immunise in compliance with priorities and possibilities. Analyse the morbidity and mortality caused by the first wave, and modify the recommendations on vaccination and the use of antivirals, if necessary. Continuously monitor the virus circulation and the appearance of influenza syndrome in the population.
	CNIPH-virology	Pursue the virologic testing of samples to identify circulating strains. Continue testing the circulating strain sensitivity to antivirals.
	CHQs	Collaborate with CNIPH in the execution of the above activities.
	MHSW	Ensure the implementation of the MCHQ activity guidelines related to the health system. Ensure the funding of the implementation of MHCQ

		guidelines within the health system.
	MAFWM	It monitors intensively the influenza virus circulation in fowl and pigs.
	Physicians of first contact	Carefully monitor the appearance of influenza syndrome in patients, notify the cases and participate in sample collection.

The pandemic period – Stage 6. The second and subsequent waves of the pandemic. *Based on experience, at a minimum one can expect the emergence of a second wave of the epidemics caused by this virus; these could break out in several countries with the onset 3-9 months after the onset of the pandemic.*

Activities: activities are to be carried out in the same manner as in the first pandemic wave, as modified based on the experience with the first epidemic wave and possible changes in vaccine and drug availability. **Activity carriers:** all activity carriers.

Postpandemic period: *WHO will declare the end of the pandemic, expected to happen in 2-3 year's time after the onset.*

Activity: As to assessment, it must deal with the overall consequences of the pandemic. Use must be made of the knowledge and experience acquired during the pandemic to control future pandemics. A renewal of and additions to the National Plan should be made in accordance with own experience and WHO guidelines. **Activity carriers:** all activity carriers.

Epidemiologic surveillance of influenza trends

The purpose of epidemiological surveillance of influenza

The purpose of epidemiologic surveillance of influenza is the observation of a potentially pandemic new influenza strain and finding an optimal health response to its emergence. In recent years, the A/H5N1/ virus has been the greatest suspect in this regard. It is known as the agent of influenza in domestic fowl and related birds, popularly called "bird flu" or technically "highly pathogenic bird influenza". Two main elements of the surveillance are:

1. Noticing the occurrence of influenza (as early in the season as possible, and even before the season[1])

([1]influenza occurring before the season signals potential emergence of a pandemic strain)
Virus identification must be enabled through sample collection. Sample collection is to continue until a satisfactory insight into circulating strains is gained. Experientially, usually there are two-three such strains, although in a possible new pandemic one could expect only one, the pandemic strain.

Based on this, inferences are made:

(a) As to the accuracy of the prediction regarding the forthcoming influenza, and about the appropriateness of the vaccine used before the season
(b) Regarding the appearance or otherwise of a new pandemic influenza strain.

2. Monitoring the development of the current influenza epidemic

This activity is aimed at observing the dynamics and intensity of the epidemic, the most affected age groups, and severity of the clinical picture through the number of influenza deaths etc., and to treat the diseased, possibly restricting visits to health institutions or their operation, and to achieve an optimal organisation of the health system generally.

Serving for the achievement of these goals is:

1. The current system (respectively the regulation-prescribed notification network for infectious diseases in the Republic of Croatia), consisting of the physicians diagnosing the disease for territorially competent epidemiologic services ranging from county public health institutes and the Zagreb Institute of Public Health, to the Epidemiology Service, CNIPH.

In keeping with the regulations, notified in this system are:
(a) All cases of influenza syndrome via individual notification card, outside the influenza season
(b) In the influenza season, individual case notification is stopped because of the change to aggregate notifications by week of illness (not of report arrival), disease outcome and age group (four age groups).

The moment of transition to aggregate weekly reporting is decided and made public by CNIPH's Infectious Disease Epidemiology Service based on the follow-up of individual

notifications, direct information from clinicians and laboratory information on influenza virus findings, about which the Service issues a special official circular letter.

2. Direct contacts with physicians and other staff capable of noticing increased morbidity are considered an important supplement to this system as they enable an early recognition of influenza notifications. Thus, each county establishes a system of phone reporting of patient clusters with the picture of influenza to the epidemiological service, which is additional to the basic system described above.

(i) To plan and organise the epidemiologic surveillance of a possible occurrence of pandemic influenza, avian influenza included, it is necessary to establish such system in each county and in Zagreb City. Next, a written plan should determine that a notification from at least two primary health care surgeries and from at least one school experiencing sudden mass class leaving by pupils is necessary.

On receiving the information about the cases suspect of influenza, the epidemiologic service should visit several typical patients at the early stage of the disease (first or second day of an illness with high temperature) and collect from them the samples needed to attempt virus isolation and virus identification. Such samples are:

- pharyngeal washing or swab in the (Hanks) transport media
- venous blood sample (the first sample)

The second sample of venous blood should be withdrawn two weeks to one month later.

The samples should be sent to the CNIPH's National Laboratory for Influenza. As they would be tested free of charge as part of the "Influenza Control" project that monitors the viral agents of influenza, the samples should be labelled accordingly.

A sample taken in a "Hanks" should be submitted in a portable freezer or similar device within a minimum transportation time. Sample collection and delivery details are prescribed in the instructions prepared by the National Laboratory for Influenza.

Any information from whatever level or part of the health system on influenza-like case clustering that is has noticed, as well as on virologically confirmed cases of influenza (positive findings) in the interval to the official publication of its presence by CNIHP's Infectious Disease Epidemiology Service in its circular letter should be forwarded to CNIPH's Epidemiology Service. The Service receives such information during 24 hours on phone number 098 22 77 53 or, during working hours, on phone number 01 468 30 04 or fax 01 468 38 77.

Information from the laboratories capable of diagnosing influenza routinely from samples originating from the patients with respiratory diseases should, in addition to being reported as described above, be sent to CNIPH's Infectious Disease Epidemiology Service in the form of weekly routine aggregate reports on positive findings and identified viral agents. This reporting lasts from 1 September of the current year to the

end of the epidemic the next. Such information is faxed to 01 468 38 77 or emailed to epidemiologija@hzjz.hr. Any laboratory influenza-positive samples must be confirmed in the National Influenza Laboratory at CNIPH.

Dissemination of the information received through the epidemiological surveillance of influenza

In nonpandemic years, the National Influenza Laboratory regularly sends the first reports on the appearance of a virus in Croatia directly to the international influenza surveillance network WHO FluNet.

In the event of finding a new, pandemic strain, such as the avian influenza A/H5N1/ or some other new strain, the National Influenza Laboratory must instantly inform CNIPH's Infectious Disease Epidemiology Service on the permanent on-duty phone 098 227 753, or on phone 01 468 30 04 (during working hours), or send a fax to 01 468 38 77. Such information will be forwarded by the method provided for in WHO documents.

Simultaneously, CNIPH's Infectious Disease Epidemiology Service sends information about this to the Ministry of Health and Social Welfare.

The same information is instantly also sent to the specimen sender and to all epidemiology services of CPHIs and of the Zagreb Institute of Public Health.

In cases of the influenza virus isolated in humans being identified by virologic laboratories as an animal virus, e.g. influenza virus A/H5N1/, CNIPH's Infectious Disease Epidemiology Service shall immediately send this information to the Veterinary Administration of the Ministry of Agriculture, Forestry and Water Management.

Conversely, if an influenza virus relevant to humans is identified in animals in the Republic of Croatia, the veterinary service shall immediately inform the epidemiologic service about it in the way prescribed by law and by the present National Plan.

Informing the public about an influenza epidemic
CNIPH's Infectious Disease Epidemiology Service shall be addressing timely information exclusively via MHCQ about the occurrence and trends of an epidemic/pandemic by every appropriate means (the media etc.).

During the epidemic, the citizenry will also receive the necessary information and advice from any other epidemiologic service within their respective sphere of action.

Epidemiologic surveillance executors for the influenza epidemic, respectively pandemic

A. Detection level: influenza-like diseases

- Outside the health system: schools, public institutions, public services, and citizens if they notice a clustering of influenza-like disease with high temperature.

- Health system: primary health care surgeries, hospitals (ca 10,000 medical teams) in accordance with regular job rules (individual case notification of the influenza syndrome, noticing of case clustering and cluster reporting (later on in the epidemic: aggregate weekly case reports).

B) Detection level: presence of a virus in the population

- influenza virus diagnostic laboratories
- laboratories diagnosing immunobiologic influenza markers in patients

(they send this information to CNIPH's Infectious Disease Epidemiology Service)

C) Information verification level (by surveys and confirmation methods)

(In the event of confirmed suspicion, the Plan requires that other links in the chain be informed):

- institute of public health epidemiologic services (of every hygiene-epidemiology/epidemiologic level)
- 113 CPHI hygiene-epidemiology outposts (teams)
- 21 epidemiologic services of CPHIs and of Zagreb Institute of Public Health
- CNIPH's Epidemiology Service.

From the basic level of observation, the information can be sent to/received by epidemiologic service of any level: these levels shall be exchanging the information within the current pattern for standing mutual communication.

Information verification consists in:

- medical theoretical verification and epidemiologic analysis
- epidemiologic survey
- drawing and sending of samples and receiving (a positive) finding from the virologic laboratory (National Influenza Laboratory).

This verification procedure is modified (shortened) if the information has been provided by a virus identification laboratory.

D) monitoring an influenza epidemic/pandemic (when an epidemic/pandemic has actually broken out)

- Basing itself on influenza notifications, the epidemiologic service undertakes daily, weekly, and monthly monitoring and reporting during the influenza season.

Epidemiologic surveillance results

The results of epidemiologic surveillance requiring measures for the protection of public health:

A) instant measures from the surveillance in the domain of MHCQ:
- informing the local (and international) public of the occurrence and circulation of influenza
- advising the public of the start of immunisation
- giving advice on when to start taking prophylactic drugs
- imposing restrictions on the activities or travel in order to protect the health of the population (e.g. a ban on visits to the threatened hospital departments etc.)

B) Besides the measures listed, any other measures referred to in the National Plan in the case of an influenza epidemic/pandemic are also based *on the results of epidemiological survey.*

Conclusion

The purpose and anticipated effects of the epidemiologic surveillance over the appearance and trends of influenza show how vitally important this segment of the overall organised response to a potential occurrence of an influenza pandemic is.

Drug-and-vaccine need assessment within the National Influenza Pandemic Preparedness Plan

Introduction

At best, waiting period from the appearance of a pandemic strain and the manufacture of a vaccine against pandemic influenza is several months long (ideally ca 6). Moreover, difficulties might crop up either in connection with producing a new vaccine or with the impossibility to make vaccine deliveries or to manufacture sufficient vaccine supplies. All this makes it imperative for the Plan to make certain provisions for a period of several months or maybe more, when no specific protection against pandemic influenza will be available.

The EU and other European countries plan to bridge this gap over by exercising epidemic control measures including the use of drugs for influenza prophylaxis, respectively treatment.

Croatia's morbidity assessment

A morbidity estimate for potential pandemics (i.e. its size) is difficult to make at a time when there is no knowing what virus will cause the pandemic, how virulent it will be, or how lethal it will prove among the diseased. The size of the pandemic, its duration and morbidity also depend on its place of origin, the interval in each state between the entry of the new virus there and the purchase of vaccine. In other countries, these estimates are based on the experience with the previous pandemics and vary between 5 to 30% of the population anticipated to fall ill. During the 1957/58 pandemic caused by a completely new viral strain (A Singapore/H2N2), CNIPH's Infectious Disease Epidemiology Service registered around 500,000 cases. Therefore, our need estimates for drugs, vaccines and other essential measures are rooted in the probability that the next pandemic could reach a similar level of registered morbidity. This assumes a number of diseased greater than the number registered, but with milder symptoms.

Vaccines and antivirals

Vaccine against interpandemic influenza strains

Since several manufacturers have registered their vaccines in Croatia, these are used each year to immunize before the influenza season. In 2005 too, the purchase of 560,000 doses of the vaccines was approved.

Because of the possibility of the interpandemic and a pandemic strain circulating in parallel, immunisation will be performed with the above vaccines even if a new viral strain emerges.

Vaccine against the influenza due to a new (pandemic) strain

The vaccine will be produced when a new influenza virus with pandemic properties emerges. For the present, this vaccine exists nowhere in the world. Pharmaceutical firms are preparing to manufacture a pandemic vaccine. It is believed that it will take a minimum of six months until the new vaccine is produced and marketed. The vaccine quantities required for a possible pandemic are planned according to the present demands by individual states. This vaccine should be reserved beforehand.

In collaboration with WHO vaccine manufacturers are preparing for vaccine production certain viruses by means of recombinant technology. These viruses could be the candidates for the next pandemic. Given that H5N1virus is also a candidate, this vaccine is one of those being prepared and should appear on the market soon. If it becomes available in the interpandemic period, poultry farm personnel would be the first to receive it.

Antivirals

Antivirals are merely a potentially efficient supplement to immunization with an influenza vaccine that could prevent contracting the disease. Their anticipated use is for the prevention and treatment of influenza during the influenza period when no vaccine against the pandemic disease will be available.

M2 protein inhibitors: rimantadine and amantadine

Rimantadine and amantadine are active against influenza A type viruses. They are used in influenza type A prophylaxis and therapy in adults and children >1 year of age. The action of these two drugs against the H5N1 virus has not been demonstrated.

Neuraminidase inhibitors oseltamivir and zanamivir

The use of oseltamivir has been approved for the treatment of adults and of children more than 1 year old and for the prophylaxis in individuals aged 13+ years. It should be used within 48 hours of the symptoms appearing. This drug has been demonstrated to shorten the duration of influenza symptoms.

The action of zanamivir resembles that of oseltamivir. It is used in the form of spray and has been designed exclusively for patient treatment.

Planned drug consumption and national stockpile requirements

Basing itself on information from CNIPH's Infectious Disease Epidemiology Service, WHO information and documents, literature data and offered planning models for drug stockpiles, as well as on the latest information from manufacturers, the Plan sets out from the following facts:

1. Oseltamivir and zanamivir are the only drugs having an effect on the H5N1 influenza. Oseltamivir has been proven effective in the prophylaxis of people

aged 13+ years, also having a proven therapeutic effect that reduces the duration of illness and alleviates symptoms in children older than 1 year. In view of the possibility that the pandemic strain could be other than H5N1, one can expect rimantadine/amantadine to be effective. These drugs should be saved primarily for use in providing prophylaxis to high-risk children. The therapeutic action of zanamivir resembles that of oseltamivir, except for the administration of oseltamivir being preventative.

2. According to the available literature, the prophylactic use of oseltamivir can be said to be much more efficient than its therapeutic one that has been demonstrated in clinical studies.

3. The available data seem to show that most states use a combination of prophylaxis and therapy, with greater focus on the therapy of the diseased but limited prophylaxis. Presumably the reason lies in therapy requiring 5 days with 2 capsules a day (10 capsules), and pre-exposure prophylaxis 6 weeks with 1 capsule a day (42 capsules).

4. No post-exposure prophylaxis is applicable during a pandemic, but only at its beginning (individual patients or smaller outbreaks). It is carried out 7 days with 1 tablet/day.

5. The prophylactic use of oseltamivir enables immunization and then the acquiring of immunity.

6. This drug should be purchased and placed in the reserve.

7. Oseltamivir has a shelf-life of 5 years (this will probably be extended to 8 years).

8. The manufacturer also offers this drug in powder form, which is less expensive (1 kg pack provides therapy for 1,000 people). This, however, requires a drug preparation process (capsulation) that should be taken up by Croatian pharmaceutical industry. Otherwise, this measure would be complex to implement (weighing the dose, solving the powder etc.). It is therefore estimated that in pandemic circumstances neither its distribution nor its utilisation would be effective.

9. In keeping with the available literature and recommendations the use of drug is recommended as follows (minimum stockpiles):

Post-exposure prophylaxis

Post-exposure prophylaxis is used at the early stage of the epidemic when individual cases of disease or smaller outbreaks (hospital, family, in an office building and similar) occur.

Such prophylaxis is administered to the close contacts of a pandemic influenza case (individuals providing care to the patient, house contacts, direct contact with respiratory secretion (droplets of saliva, cough, sneezing; bodily fluids and excretions (faeces) from a highly suspect or confirmed case).

Prophylaxis is only undertaken in people aged above 13 years. In children, the oseltamivir prophylaxis is not applied. Prophylaxis should be started within two days of the exposure.

Adults: In adults, the oseltamivir prophylaxis involves taking 7.5 mg oseltamivir a day for 7 days.

In children more than 1 year old (1-9 years) use can be made of amantidine prophylaxis. The dose (therapeutic and prophylactic) is 5 mg/kg body weight, but caution must be exercised not to exceed 150 mg/day (FDA and MMWR).

For children aged above 10 days and adults, the daily dose is 200 mg/day (100 mg twice a day).

However, in children with a body weight below 40 kg, the amount to prescribe irrespective of their age is 5 mg/kg body weight.

As amantadine is an ineffective prophylactic in this subtype of influenza, such prophylaxis shall not be undertaken in the case of an H5N1 pandemic.

The number of people expected to receive the post-exposure protection is 1,000.

Pre-exposure prophylaxis

Pre-exposure prophylaxis may be administered to the staff of those operative services whose operation is essential in the case of pandemic. It should start for category 1 staff after the first proven case of pandemic influenza in the country. In the case of pandemic strain spreading in the country, the pre-exposure prophylaxis is to be administered for category 2 staff as well. This prophylaxis may be run a maximum of six weeks.

Estimated absolute minimum of people to receive the pre-exposure chemoprophylaxis

Operative category 1 encompasses 3,200 people.
Operative category 2 encompasses 11,200 people.

Category 1 + category 2 = 14,400 people or sixty-one thousand 10-capsule boxes.

Treatment

- treating the patients at high risk of complications

- treating the groups according to the epidemiologic indicators during the pandemic.

The administration of therapy is envisaged for persons above 1 year of age. For children aged 13+ years and adults, the therapeutic dose of oseltamivir is 75 mg twice a day for five days. The zanimivir therapy consists of 2x5 mg for 5 days. Zanimivir is taken by inhaling it.

Epidemiologic simulation foresees that a minimum of 250,000 people would receive the necessary antiviral treatment. This amounts to a minimum of 250,000 therapeutic doses to keep in stock for the event.

Immunising with a vaccine prepared from the pandemic influenza strain

As the vaccine against the pandemic strain will be available in limited quantities, the minimum vaccination coverage shall involve the groups of people expected to run a greater risk of complications (a priority), and the people working for the services that are essential to maintaining vital functions of the state. To reduce the consequences of the first wave of pandemic influenza, an estimated minimum of 2,000,000 doses of the new vaccine would be needed (two doses per person are envisaged).

Vaccinating the whole population would be ideal. It is not essential for the state to ensure a free vaccine for the entire population, but to reserve the necessary quantities of the vaccine with the manufacturer or, if possible, to offer a domestic vaccine producer to manufacture a portion of the production run.

Other vaccines

As regards nonpandemic influenza, everyone at heightened risk will be vaccinated. This vaccination is to cover the poultry farm personnel as well.

If the pandemic occurs outside the Republic of Croatia, the at-risk groups (about 60,000 people) will be administered the standard vaccine.

If a vaccine against the H5N1 avian influenza becomes available in the meantime, it is recommended to purchase this vaccine for poultry farm workers and for the persons who are certain to come into contact with the influenza virus (virologists, veterinarians, i.e., around 700 people).

Pneumococcal vaccine

All people at risk are to be vaccinated with the pneumococcal vaccine.

If the pandemic breaks out, anyone aged 65+ years will be vaccinated, as well as the people who have been ill for more than two years (chronic diseases: constrictive heart

lesion, diabetes, chronic alcoholism, chronic disease of the liver, immunodeficient patients).

Protection with anti-avian influenza drugs (highly pathogenic strains, such as H5N1)

In the case of avian influenza (H5N1) and other strains infective for humans, post-exposure prophylaxis with oseltamivir should be administered to the people having a contact with poultry.

Antipyretics

The use of antipyretics such as paracetamol shall be indicated for influenza. If influenza is suspected in children, acetyl-salicylate is contraindicated. Stockpiling of these drugs is assumed not to be essential, as they will be available in pharmacies during the pandemic.

Medical equipment

Health facilities and physicians in charge should see to it that stockpiles of drugs and accessories like needles and injections are sufficient for symptomatic therapy.

Antibiotics

In view of bacterial complications being common in influenza, an increased use of antibiotics should be planned for a situation where a high incidence of such complications as pneumonia is expected. An unfailing source of supply of antibiotics (with antistaphylococcal action spectrum) should be secured.

Personal protection devices

Personal protective devices are designed for the health workers providing personal health care, inclusive of the epidemiological team that will be carrying out field investigations. It is estimated that an appropriate quantity of personal protection devices should be stockpiled for this and other emergencies.

Organizing the treatment and chemo prophylaxis

Primary health care physicians shall give CPHIs and the Zagreb Institute of Public Health figures on the people at risk of complications from influenza. In keeping with these figures, Institute of Immunology will deliver appropriate quantities of drugs to CPHIs and to the Zagreb Institute of Public Health to distribute among physicians of first contact. This procedure shall unfold according to the stage of the pandemic. All drugs should be stocked in one place and well guarded.

Drugs for treatment kept at CNIPH shall be forwarded, at the appearance of individual cases, to CPHIs and to Zagreb Institute of Public Health. On pandemic strain becoming widespread, these drugs shall be distributed among primary care physicians.

Post-exposure chemo prophylactics shall be stored at CNIPH and forwarded, as needed, to CPHIs and to Zagreb Institute of Public Health (to protect the unaffected from the diseased in individual cases of pandemic influenza).

Pre-exposure protection with drugs

The figure on the number of people to receive in individual branches of economy the pre-exposure protection must be submitted to CPHIs and to the Zagreb Institute of Public Health.

Detailed drug distribution and drug administration plans must be worked out.

Patient management algorithm for influenza suspects

Presence of influenza symptoms — No — It is not influenza

Yes

Clinical influenza

- Patient stable and free of co-morbidity* — Send patient home for self-treatment
- Patient stable and having co-morbidity/other risk* — Oseltamivir therapy and discharge home
- Additional management necessary
  - Inpatient/infectological treatment — Co-morbidity-free pneumonia*
  - Vague diagnosis, extra investigations — Therapy for pneumonia and discharged home

Pneumonia with co-morbidity* — Under observation at hospital

Acute confusion

Metabolic disorder

Respiratory disorder

Acute cardiac disorder

Hospitalisation — Discharge

Figure 2 Algorithm for managing an adult patient (>18 years) suspect of having influenza

Patient screening can be done in surgeries, clinics, and, if necessary, at other sites. When possible, hospitals should provide a space separate from other emergency admission rooms in order to screen the patients who are suspect of having influenza.

*Co-morbidity/other risk:

- aged 65 years or above
- pregnancy
- chronic lung disease (e.g., chronic obstructive lung disease, cystic fibrosis,…)
- congestive heart failure
- kidney failure
- immunodeficiency (either due to the underlying disease or to therapy)
- haematologic disorders (anaemia, haemoglobinopathy)
- diabetes
- liver disease
- persons on long-standing therapy with acetylsalicylates (increased risk of Rey's syndrome)

Acute respiratory infection accompanied by

1. symptoms of respiratory insufficiency[1] and/or
2. co-moribidity[2] and/or
3. positive tests for lower respiratory tract infection

- hematologic disorders (anaemia, haemoglobinopathy)
- diabetes
- liver disease
- individual on long-term therapy for acetylsalicylates (increased risk of the Rey syndrome)

No.

Patient discharged home with parents receiving the education[3]

Yes

Patient management at hospital

Hospitalisation

Figure 3 Algorithm for managing children (<18 years) suspect of having influenza

[1] symptoms of respiratory insufficiency and other severe symptoms:

- Difficulty breathing (drawing in of nostrils, intercostals spaces or jugulum at inspiration, quick breathing, stridor)
- Cyanosis and/or disorders of circulation
- Continual vomiting
- Disorder of consciousness (confusion, lethargy)
- Convulsions
- Tense fontanel
- Stiff neck, photophobia
- High body temperature or low body temperature
- More severe dietary or sleep disorders.

[2] co-morbidity and other risks for complications of influenza

- Chronic cardiac or pulmonary disease
- Chronic metabolic diseases (diabetes, …)
- Malignant diseases
- Immunodeficiencies (either due to the underlying disease or to therapy)
- Kidney disease

- Anaemia, haemoglobinopathy
- Children on long-standing therapy with acetylsalicylates (increased risk of Rey's syndrome)

[3] educating a parent/guardian to:

- Maintain hydration
- Keep check on heightened temperature (avoidance of salicylates because of Rey's syndrome!)
- Monitoring the child's condition
- Immunisation/prophylaxis of high-risk individuals
- General measures for the prevention of infection (hygiene of hands, disposal of used handkerchiefs, avoidance of unnecessary contacts, …)

Virologic diagnostics

Activity classified by stages

WHO's stages 1, 2 – Interpandemic period

1. Testing

Normal laboratory activities are carried out which include all laboratory studies from rapid diagnostic methods to isolation on cell cultures and on embryonic chicken eggs.
Nasopharyngeal smears are generally recommendable but all kinds of specimen are accepted; in young children, it is best to collect a nasal washing.
Any samples collected in the field will be analysed by arrangement with CNIPH's Epidemiology Service, and irrespective of what tests have been ordered, the analysis shall proceed as recommended by the head of the National Centre taking account of the need for differential diagnosis.
In view of the possibility of neuroaminidase inhibitor drugs being used preventively and on a large scale, it is necessary to organise a training course at one of WHO laboratories where a technology for testing drug resistance in relation to the influenza virus would be adopted.
The preparation and expansion of the current workspace and human resources
2. Surveillance
Monitoring and weekly reporting to CNIPH's Epidemiology Service and to WHO Reference Centres is to cover all demonstrated respiratory viruses.
3. Communication
Of necessity, the Centre's readiness must be in the form of mobile phones.
It should participate in the Preventive Health Headquarters activity, in that of the Appointed Committee on Monitoring and Surveillance, and in "bird flu" prevention.

WHO's stages 3, 4 – New influenza virus demonstrated in one or more people

1. Testing
The same activity as in stages 1 and 2 should continue, accompanied by an intensification of all diagnostic activities
2. Surveillance
The same activity as in stages 1 and 2 should continue, coupled with the possibility of using several virologic teams on a 24-hour basis for emergency diagnosis requirements.
The monitoring and daily reporting of CNIPH's Epidemiology Service and of WHO Reference Centres is to cover all demonstrated respiratory viruses.
3. Communication
The same activity as in stages 1 and 2 should continue, combined with a more active follow-up of news from WHO and forwarding them urgently to CNIPH's Epidemiology Service.

WHO's stage 5- Interhuman mode of transmission

1. Testing
The same activity as in stages 3 and 4 should continue, accompanied by an intensification of all diagnostic activities.
2. Surveillance
The same activity as in stages 3 and 4 should continue, accompanied by the National Centre taking part in the activity of the International Pandemic Committee.
3. Communication
The same activity as in stages 3 and 4 should continue, plus following up more closely the news from WHO and forwarding them urgently to CNIPH's Epidemiology Service, and the introduction of "null reporting".

WHO's stage 6

1. Testing
The same activity should continue as in stage 5 accompanied by an intensification of all diagnostic activities.
2. Surveillance
The same activity should continue as in stage 5 accompanied by participation of the National Centre in the work of the International Pandemic Committee.
3. The same activity as in stage 5 should continue, plus following up more closely the news from WHO and forwarding them urgently to CNIPH's Epidemiology Service

Postpandemic period

It is a return to the interpandemic period.

Microbiologic tests to be performed at the laboratories of the Respiratory Virus Diagnosis Unit laboratories with the National Centre

Legend
ISOLATION – isolating the virus in cell culture and in fertilised chicken eggs
DFA – direct fluorescence test
IFA – indirect fluorescent test
ICHG – immunochromatography test
HI – haemagglutination inhibition test

Sample collection

Blood: 5 ml in a sterile test tube

Smear (of upper respiratory tract)

- take a smear within the first three days of the disease onset
- take a smear both from the nose and throat
- place both smears in the same test tube with a (Henks) transport medium.

NW (nasal washing) – it should be taken from younger children by using a mucus extractor with the prior application of 1 mL sterile physiologic solution.

Storage - until sending them to a laboratory all samples should be stored in a cool place ($+4^0$C) and transported urgently (maximum of 24 hours) secured from drying (Henks transportation medium) and from heating (tightly closed in a thermos with ice).

Tests:

DFA – for virus type A influenza
DFA – for virus type B influenza
DFA – for respiratory syncytial virus
DFA – for adeno viruses
DFA - for parainfluenza virus type 1
DFA – for parainfluenza virus type 2
DFA – for parainfluenza virus type 3

IFA – for virus type A influenza
IFA - for virus type B influenza
IFA - "screening" test for respiratory viruses

ICHG – serologic demonstration (IgM, IgG, IgA) to SARS-COV
ICHG – demonstration of antigen to SARS-COV

HI – serologic evidence of antibody to influenza type A/H_1N_1/ virus
HI – serologic evidence of antibody to influenza type A/H_3N_2/ virus
HI – serologic evidence of antibody to influenza type B/2 virus

Isolation of:
- influenza virus type A/H_1N_1/
- influenza virus type A/H_3N_2/
- influenza virus type A/H_5N_1/
- influenza virus type B/2/
- respiratory syncytial virus
- adenovirus (24 types)
- parainfluenza virus (3 types)
- SARS-COV

Laboratory for protection from risk 3+ or 4 group micro-organisms

All laboratory staff must possess a document testifying that they have been trained to work in a laboratory of this biosafety level.

All procedures used on infectious material are carried out in biosafety cabinets while wearing the appropriate protective clothing.

A) EQUIPMENT

1. Class III biosafety cabinet
2. Input-output type double-ended autoclave
3. A centrifuge with protection from the spread of aerosol (+4^{0}C).

B) SPACE

It is isolated and separate from any points of contact with other rooms; when entering this space a treble door must be used.

The walls and floors must be covered with ceramic tiles to facilitate disinfection with chemical agents.

Each laboratory must have a wash-basin designed for hand washing with photocell-operated taps.

A door for automatic opening (with a photocell and a card)

Compartment with toilet block for changing protective clothing, footwear and garments

Closed and sealed windows with air-conditioners providing air circulation

A ventilation system that directs air current towards the areas “of higher risk of aerosols”

At the exit, the air must be filtered by HEPA filters.

Centrifugals and other equipment positioned at sites where the generation of aerosol seems likely are also connected with the air drainage system through HEPA filters.

9. First aid kit with a special eye washing solution included must be available within the laboratory

Nonreflecting light fixtures must be installed.

A record of all procedures done in biocabinet III must be kept, with the cabinets checked and serviced regularly.

The room must have a negative air pressure.

Autoclaving of the infectious material is to take place in a double autoclave. If the infectious material is transported outside the laboratory, it must be stored in safety containers.

Biosafety level four requires building a separate access.

Avian influenza surveillance and control

1. Routine surveillance of avian influenza

Fowl plague disease (further herein: avian influenza) figures on the list of diseases whose prevention and control are of interest to the Republic of Croatia in accordance with the Veterinary Medicine Act (Official Gazette of the Republic of Croatia, OGRC, 70/97, 105/01, 172/03).

Avian influenza figures on the list of the diseases that are notifiable both in the case of suspicion of the disease and in confirmed cases of the disease. This has been prescribed by the Mode and Procedure for Notification of Suspicion and Cancellation of Infectious Animal Disease and the Requisite Forms Form and Contents Regulation (OGRC 179/04).

In 2005, the Veterinary Administration did not receive a single notification of suspicion of avian influenza from the owners/holders of birds, certified veterinarians or county veterinary inspectorates under the above regulations.

2. Measures to reduce the risk of emergence of avian influenza (an import ban, sanitary and other measures on farms, health education and similar)

Based on Article 11, Veterinary Medicine Act, the minister of agriculture, forestry and water management may decree special conditions for, limitations or ban on the import and transit of animals and animal products with the view to preventing the introduction of animal diseases and zoonoses in the Republic of Croatia.

Based on the above provision, there is in force a Decree Banning the Import into Croatia or Transit across Croatian territory of Poultry and Poultry Products to Prevent the Introduction of Avian Influenza (OGRC 104/05). Importation to and transit across Croatia of the following consignments is banned:

(a) live poultry and feathered gamebirds
(b) one-day poultry
(c) fertile and market eggs
(d) semen of poultry and feathered gamebirds
(e) fresh and frozen meat from poultry and feathered gamebirds
(f) meat products from poultry and feathered gamebirds
(g) products of animal origin (from birds) intended for animal feeding, industrial use or farming applications.

Based on a valid Decree, imports have been banned from the countries as follows:

1. Hong Kong
2. Indonesia
3. Japan
4. Republic of South Africa
5. Republic of Korea
6. Cambodia
7. Kazakhstan
8. China
9. Laos
10. Mongolia
11. Russia
12. Thailand
13. Vietnam

The ban also covers consignments originating from other states if they are transited across the territories of the states listed.

Recommendations on the prevention of avian influenza to poultry owners on family farmsteads and in intensive poultry growth facilities specify, in addition to the strict implementation of general non-specific measures, making the contact between domestic fowl and wild birds impossible. Next, they stipulate bird flock renewal from strictly controlled conditions for growth, and a strict application of biosafety measures on the farm.

3. Urgent reporting of avian influenza case suspects to the epidemiologic service

In the case of a zoonosis, Veterinary Office is obliged, in accordance with the Veterinary Practice Act, to report the emergence of the disease to a governmental body competent for health.

4. Virologic diagnosis

Using the official methods, Croatian Veterinary Institute's Poultry Centre does laboratory investigations of the diagnostic material to identify the agent of avian influenza.

The laboratory diagnosis of avian influenza at Croatian Veterinary Institute's Poultry Centre is established by virus isolation from chicken embryos and by assessing its pathogenicity in chickens 6-8 weeks old. Isolated viruses are forwarded for detailed typing to the OIE and to the EU Reference Centre for Avian Influenza – Central Veterinary Laboratory New Haw, UK – Weybridge, Surrey KT 15 3NB, United Kingdom.

Whereas serologic diagnosis of avian influenza at the Poultry Centre is based on gel immunodiffusion, for chicken and turkeys the ELISA method is also used. Positive sera for viral subtype identification are sent to the OIE and to the EU Reference Laboratory for Avian Influenza at Weybridge.

5. Intensifying bird surveillance by "screening" for avian viruses

In connection with the current epizootic situation of avian influenza globally and in Europe especially, the Veterinary Administration of MAFWM plans to set the serologic testing of poultry and wild birds for the presence of an avian influenza agent as a legal requirement.

6. Epizootic control measures in the case of an avian influenza outbreak

In the case of raised suspicion and confirmation of the occurrence of avian influenza, the following measures shall apply:

<u>Notification of infectious disease</u>

- If either the infectious disease avian influenza occurs or so do the signs based on which a suspicion can be raised that an animal had contracted avian influenza or died of it, the animal owner must report this instantly to the Veterinary Office, a veterinary organisation, veterinary station or a private veterinary clinic. This shall be done in accordance with the Regulation on the Mode and Procedure of Notifying the Suspicion and Cancelling of Animal Infectious Disease and for Prescribing the Method and Form of Prescribed Forms (OGRC 179/04).
- The animal owner is to restrict immediately the movement of the animal that he suspects to be ill with avian influenza or to prevent human and animal contacts with its carcass until veterinary examination, as well as carry out the ordered or prescribed necessary measures after the examination
- On learning of an animal case suspect of the animal disease avian influenza, any veterinary employee should notify the Veterinary Office about the suspicion of the animal infectious disease.

- Upon receiving a notification or learning about a case suspected of avian influenza, the Veterinary Office should order a veterinary organisation, veterinary station and private veterinary clinic to:
  - determine whether the suspicion of avian influenza is justified
  - immediately apply pertinent veterinary health measures to prevent the spread of the infectious disease: these the animal owner is obliged to carry out immediately
  - in the case of grounded suspicion of there being a case of avian influenza, veterinary employee should take a proper diagnostic sample and submit it for examination to Poultry Centre, Croatian Veterinarian Institute
- There is considered to be a suspicion of infectious disease when two or more cases of disease or death with the same or similar signs happen in a flock, courtyard, other place or space where animals stay temporarily or permanently, respectively when an animal dies suddenly for no apparent reason

Confirmation of an avian influenza outbreak

- When either the diagnosis of avian influenza is established or a suspicion of avian influenza set, it is the responsibility of the Veterinarian Office to notify the Veterinary Administration in the prescribed way of its suspicion, respectively established infectious disease
- Notification in the case of especially dangerous infectious diseases: the notification of avian influenza must be done urgently and can be done orally via phone or other means, with a written notification submitted subsequently
- In its area, the Veterinary Office is obliged to inform of the outbreak of avian influenza corporate and physical persons who carry out the veterinary activity, as well as the competent veterinary service of the Croatian Army
- In the case of an avian influenza outbreak, the Veterinary Office must also inform CNIPH's Epidemiology Service.

Cancellation of the presence of infectious diseases

- Veterinary Office is obliged to send to the Veterinary Administration the cancellation of the infectious disease avian influenza in the prescribed manner and inform about it veterinary organisations, veterinary stations, private veterinary clinics and the competent Veterinary Service of the Croatian Army
- An infectious disease is considered to have ended when after the treatment and recovery, eutanasia, slaughter or death of the last diseased animal and on completion of the final disinfection, respectively disinsection and deratisation the longest period of incubation for that disease had passed, respectively on completion of the prescribed serologic investigation if it has been prescribed.
- The mode, procedure, as well as the form and contents of the form for infectious disease notification/cancellation, as well as the signs based on which one consider that the disease has occurred, are set by the Regulation on Notification of Suspected Animal Infectious Disease, Notification and Cancellation of Animal Infectious Disease, and the Form and Content of Prescribed Forms (OGRC 179/04).

Laboratory diagnosis

- In identifying the agent of avian influenza, Croatian Veterinary Institute's Poultry Centre performs the laboratory diagnosis of the diagnostic material by using the official methods.

Infectious disease control and eradication measures

- On establishing the occurrence of avian influenza and for the duration of avian influenza danger, the competent veterinary inspector may decide, depending on the level of danger and agent pathogenicity that the execution of one or more of the following measures should follow:
  - isolation of sick animals and keeping them separate from healthy animals

- banning or limiting the movement of animals
- forbidding the holding of animal fairs, exhibitions, sporting competitions and other public reviews, and banning the operation of marketplaces and conveyance of animal herds
- a ban or restriction on trade in animal products, feed and other objects capable of transmitting an infectious disease
- euthanasia for sick animals and those suspect of being infected
- drawing up a list of animals and labelling them in a special way
- banning or limiting the production of animals over a specified period
- banning the issuance of certificates on the health status and origin of animals, of health certificates attesting the wholesomeness of animal products, and of other documents prescribed by the Veterinary Practice Act
- declaring a temporary ban on the operation of the facilities where animal products capable of transmitting the disease are manufactured, processed, stored and marketed
- in special circumstances, natural disasters or larger-scale epizooties, in order to control and eradicate infectious diseases the minister can also decree that other measures and actions be taken, which are not stipulated by the Veterinary Practice Act.

Infected area/an area threatened by infection

- defining of the infected area or an area threatened by infection is undertaken by the Veterinary Office or by the director, Veterinary Administration.

Organizing veterinary teams for control of especially dangerous infectious diseases

- when an infectious disease occurs that is capable of causing substantial economic damage, and when there is a threat of an especially dangerous infectious disease envisaged in Article 8, Veterinary Practice Act, the Veterinary Office shall nominate groups of veterinarians and other professionals in the epizootic area. It will charge them with the implementation of measures for the control and eradication of the infectious disease. Depending on the level of threat, Veterinary Office may request the participation of civil defence
- if the infected or threatened area is deficient in veterinarians to effectively control the disease, the director can mobilise the necessary number of veterinarians and other professionals and assign them to the infected or threatened area

Participation of the Croatian Army

- On the proposal of the Veterinary Administration's director, the MAFWM minister may — in order to render impossible the introduction and spread of certain especially dangerous infectious diseases listed in the Veterinary Practice Act, and to enable the undertaking of control measures — request the Croatian government to determine the way in which Croatian Army units will participate in the implementation of the measures restricting or banning the movement of

people and animals from/into certain areas and, if necessary, parts of the Republic of Croatia's border.

Animal euthanasia or slaugther measures designed to control an infectious disease

- in the case of avian influenza outbreak, the "stamping-out" method should be used as a measure to prevent the spread of the disease. This involves:
- immediate and undelayed euthanasia of all animals on the infected farmstead, which should be done under the official supervision and in a way preventing the spread of the avian influenza agent during their slaughter and transportation
- officially supervised detection and harmless removal of the meat of the poultry slaughtered in the interval between the probable introduction of the avian influenza agent into farmstead and the start of implementation of the measures ordained
- euthanasic measures and harmless removal of the infected animals and of those exposed to the infection, as well as the destruction of infected objects shall be ordained when the infectious disease is incapable of being controlled effectively and without the risk of it spreading by the other measures prescribed by the Veterinary Practice Act, or when the implementation of other measures for its control is uneconomical
- the measures are ordered by the director of the Veterinary Administration or by the veterinary inspector whom the director has empowered to do so.

Police department staff participation

- officials of the police department in the infected or threatened area provide assistance within their competence to the Veterinary Office on its demand, and help in marking off the infected sites and areas, limiting the movement of animals, banning the movement of animals and humans in the infected area, as well as in the implementation of other measures for the protection of animal health from infectious diseases.

Croatian Army Veterinary Service

- the Veterinary Service of Croatian Army shall take measures for control and prevention of infectious diseases in the animals serving the needs of the Croatian Army, reporting this, the measures taken and the end of the infectious disease outbreak to the competent Veterinary Office.

7. (Post-exposure) protection for the individuals who had been in contact with diseased poultry

We consider that in the event of avian influenza, several hundred poultry owners, poultry manufacturing industry workers, veterinarians and local inhabitants on the site of infection could be exposed to the disease.

8. Potential exposure of the virologist team to avian influenza (for planning their pre-exposure protection with drugs)