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## INFLUENZA EPIDEMIOLOGY IN CROATIA AND PREPARATIONS FOR POTENTIAL PANDEMIC

### EPIDEMIOLOGIJA INFLUENCE U HRVATSKOJ I PRIPREME ZA MOGUĆU PANDEMIJU

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#### Summary

Surveillance of influenza in Croatia is based on notification of disease/death due to communicable diseases that are reported within 24 hours (during the influenza season weekly aggregated reports are submitted) to the Epidemiology Service of the Croatian National Institute of Public Health (CNIPH). Field investigation of each cluster is conducted and samples are sent to the CNIPH National laboratory for influenza. The registered influenza morbidity in Croatia amounts to up to 191,000 cases annually, oscillating, in the interpandemic period, from several thousand to over 190,000. Average annual notification rate during last five years was 168/10000 inhabitants. Based on health service notification in the season 1957/58, Asian influenza pandemic A/Singapore/H2N2 caused illness in more than 500,000 people. The Hong Kong pandemic influenza (A/Hong Kong/H3N2) was registered in Croatia in the 1967/68 and 1969/70 season. Total number of notified influenza cases during that period was 582,000 people (14% of inhabitants). During the Hong Kong influenza pandemic morbidity higher than 1,000/10,000 inhabitants was recorded both in children aged 7-19 years and in persons aged 20+ years. The Preparedness Plan for Pandemic influenza is based on historical morbidity data in previous pandemic influenza outbreaks in the country. The brief overview of preparedness plan was given using the phases of interpandemic and pandemic period according to the latest agreed definitions published by the WHO.

**Key words:** Influenza; Epidemiology; Croatia; Preparedness plan; Pandemic

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## INTRODUCTION

A disease we encounter every year, influenza occurs in wintertime with regular seasonality. In humans, influenza is caused by type A type B and type C viruses. There is antigenic difference among virus types A, B and C. Humans may become infected with each of these viral types. Virus type A has the highest epidemic potential because it experiences frequent antigenic changes. In virus type B, the epidemic potential is lower. Antigenically, it is relatively stable, with in principle the past influenza B conferring permanent immunity. Virus type C-caused influenza passes as a mild infection, which in most cases goes by unrecognised. Influenza A subtypes are classified by the antigenic properties of the surface glycoproteins, the haemagglutinin (H) and the neuraminidase (N). Frequent mutation of the genes encoding the surface glycoproteins of influenza A and B viruses results in emergence of variants (antigenic drift). Emergence of completely new subtypes (antigenic shift) occurs at irregular intervals and only with type A viruses. Since no one is immune to a thus changed virus, a pandemic may develop that is capable of global spread. Either in the past or now, type-A viruses circulated in the human population whose surface haemagglutinin is H1, H2 or H3, with only the viruses carrying the N1 and N2 neuraminidase recorded until now [1-10].

### Recent history of the human influenza virus

It is hypothesised that virus A/H3 was in circulation until 1918. The virus change, which took place then, has resulted in a completely new virus, A/H1N1. It has caused a pandemic known as the "Spanish flu". The next big change in the virus occurring in 1957 led to the emergence of A/H2N2, which has caused a pandemic of the so-called Asian flu. The A/H1N1 virus vanished from circulation. A new, changed virus, A/H3N2 set out from Hong Kong in 1968. It too went round the world, though causing lower morbidity and mortality, as it changes haemagglutinin only, while viruses with the same neuraminidase (N2) did circulate in the population, thus generating partial immunity. This time round a virus circulating previously was also squeezed out of circulation in the human population. Despite the belief that this crushing out is an essential regularity in the appearance of a pandemic strain, 1977 saw a change in this rule. Then the virus A/H1N1 SSSR emerged, which did not push the A/H3N2 virus out, resulting in circulation of this two viruses at the same time [1-3,6,9-11].

Several interesting events are associated with this last virus. One is the emergence of the H1N1 swine virus in an American military camp preceding it. As the swine virus had infected a smaller number of people, a vaccine was produced against this strain, and large proportion of US population was vaccinated because the possibility of wide spread of the new H1N1 virus. The virus did not spread widely. The next year though,

a new virus - H1N1, emerged, which was identical to the H1N1 virus that had circulated until 1957 [1,2]. This raises the suspicion that it may have originated from some laboratory where it had been kept all those years.

Despite spreading around the world and being in circulation even today, this virus has not caused a pandemic on the scale of the Spanish flu since. When in 1978 it appeared in Croatia 123,000 cases were registered, which is within the limits of the oscillations recorded during inter-pandemic periods.

## MATERIALS AND METHODS

Croatia's monitoring of its epidemiologic situation is based on notifications of disease/death due to communicable diseases that are reported within 24 hours to the epidemiology service of County Public Health Institutes and of Croatian National Institute of Public Health (CNIPH). Before the influenza season, the Epidemiologic Service is immediately advised by phone of any influenza-like case clustering. It initiates diagnostic procedures (respiratory viruses isolation, including influenza) in collaboration with CNIPH's National Influenza Laboratory aimed at establishing as early as possible the appearance of influenza in the population. National Influenza Laboratory is part of Flu-net laboratory network and it is under regular supranational supervision performed by the WHO and European Referral Laboratory for Influenza. All field epidemiologists are equipped with swabs and transport media for respiratory viruses. Upon identifying the virus present in the population, we record the patients by age group using a group 7-day notification form. Influenza morbidity data between 1957/58 and 2004/05 season are presented. The report will also describe the Preparatory Plan for Influenza Pandemic

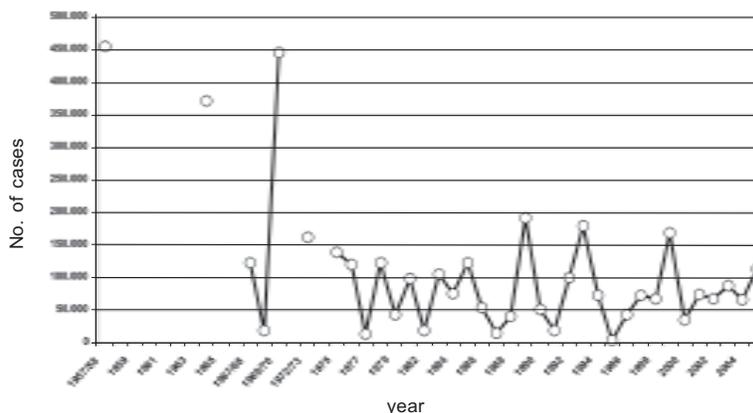


Fig. 1. Influenza cases in Croatia 1957-2005

Table 1. Influenza virus strains circulating in Croatia 1957-2005

Year	Strain	Year	Strain
1957/58	A/Singapore/H2N2	1988	B/Victoria
1964	?	1989	A/Sichuan/H3N2 A/Taiwan/H1N1
1967/68	A/Hong Kong/H3N2	1990	A/Shangai/H3N2
1969	A/Hong Kong/H3N2	1991	A/Taiwan/H1N1 B/Victoria
1969/70	A/Hong Kong/H3N2	1992	A/Taiwan/H1N1 B/Beijing/H3N2 B/Panama
1971	B	1993	A/Beijing/H3N2 B/Panama
1972/73	A/England/H3N2 + B	1994	A/Hong Kong/H3N2 A/Shangdong/H3N2
1974	B	1995	A (serogicaly)
1975	A/Port A/Chalmers/H3N2	1996	A/Singapore/H1N1
1976	A/Victoria/H3N2 + B	1997	B/Beijing
1977	A/Victoria/H3N2 + B	1998	A/Wuhan/H3N2
1978	A/Texas/H3N2 A/SSSR/H1N1	1999	A/Sydney/H3N2 B/Beijing
1979	A/SSSR/H1N1	2000	A/Sidney/97/H3N2
1980/81	A/Bangkok/H3N2 + B A/Brazil/H1N1	2001	A/H1N1
1982	B/Singapore	2002	A/New Caledonia/H1N1 B/Sichuan
1983	A/Bangkok/H3N2 A/Philippines/H3N2	2003	A/H1N1 A/H3N2 B
1984	B/Singapore B/SSSR A/H1N1 (serologicaly)	2004	A/Zagreb/H3N2/488/04 (similar to Johannesburg)
1985	A/Chile/H1N1 A/Philippines/H3N2 B (serologicaly)	2005	A/ N.Caledonia/H1N1 A/H3N2/Fujian/Wyoming B/Shangai
1986	A/Inverness/H3N2 A/Hong Kong B/Victoria		B/Hong Kong
1987	A/Singapore/H1N1		

drawn up by CNIPH's Infectious Disease Epidemiology Service's epidemiologists in collaboration with members of the Medical Prevention Headquarters appointed by the Minister of Health and Social Welfare.

## RESULTS

### Influenza morbidity data between 1957/58 and 2004/05

The registered influenza morbidity in Croatia from 1971 to 2005 amounts to up to 191,000 cases registered annually (424.4/10000 inhabitants), oscillating, in the interpandemic period, from several thousand to over 190,000. During the circulation of A/England/H3N2 and influenza B circulated in 1972/73, A/Sichuan/H3N2 and A/Taiwan H1N1 in 1989, and A/Beijing/H3N2 and B/Panama in 1993, as well as A/Sidney/H3N2 and B/Beijing in 1999, we registered more than 160,000 patients. Average annual notification rate during last five years was 168/10000 inhabitants (Graph 1, Table 1).

In the season 1957/58, Asian influenza A/Singapore/H2N2 caused illness in more than 500,000 people registered in the Health Service (Table1, Graph 1).

The Hong Kong influenza (A/Hong Kong/H3N2) was registered in Croatia in the 1967/68 season when 123,000 people fell ill. In the spring of 1969, more than 19,000 people became ill of the same agent, with this influenza culminating in more than 440,000 cases during the 1969-70 transition. The total number of notified influenza cases during that period was 582,000 people (14% of inhabitants) (Graph 1, Table 1).

Table 2. Age-specific incidence rates 1969-2002

Season	Total number of cases	Age group 0 – 6	Age group 7 – 19	Age group 20 +	
1969-70	445.809	838	1.051	1.037	Hong Kong
1991/92	97.952	358	674	75	
1992/93	174.802	492	1.146	373	
1993/94	73.179	215	328	106	
1994/5	4.330	16	17	6	
1995/96	42.930	142	236	49	
1996/97	73.464	184	341	105	
1997/98	67.707	272	264	97	
1998/99	169.265	414	590	299	
1999/00	34.666	74	86	71	
Season	Total number of causes	Age group 0 – 6	Age group 7 – 19	Age group 20 – 59	Age group 60 +
2000/01	70.345	244	436	76	39
2001/02	67.553	226	366	91	40

We have constantly registered the highest influenza morbidity in 7-19-year-olds. During the Hong Kong influenza pandemic morbidity higher than 1,000/10,000 inhabitants was recorded both in children aged 7-19 years and in persons aged 20+ years. Constantly we register the lowest morbidity at the oldest age (Table 2). However, because of the increased risk of complications at that age, (based on hospitalizations and influenza mortality CNIPH data) vaccination is recommended for the oldest population. The number of people immunised against influenza in Croatia is higher every year. In 2005 the influenza vaccination rate was about 133/1,000 inhabitants.

Table 3. Influenza age-specific morbidity during 2004/2005 season

Age	No of cases	%	Incidence/10000
0-6	12904	11,4	321
7-19	50077	44	589
20-59	44291	38,9	160
60+	6514/1	5,7	100
Total	113786/1	100	243

More than 113,000 influenza cases were recorded in its 2004/05 season. During the outbreak four viruses were in circulation: A/N.Caledonia/H1N1, AH3N2/Fujian/Wyoming, B/Shangai and B/Hong Kong. The group aged 7-19 years had a morbidity of 589/10,000 population of that age. In the youngest patients (up to 6 years old), the morbidity rate was 321/10,000. The morbidity rate declined with age, being 160/10,000 in the age group 20-59 years, and 100/10,000 in the oldest (60+ years) (Table 3). We constantly register influenza deaths in the oldest age group.

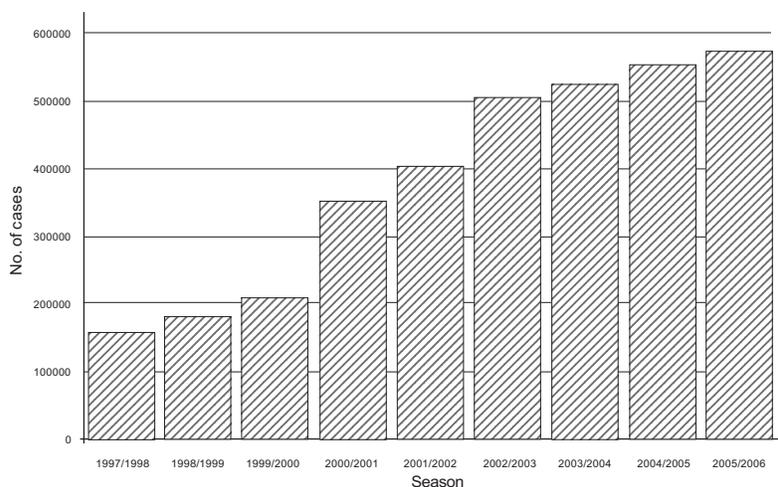


Fig. 2. Distribution of vaccine in Croatia 1997-2005

## Preparing for influenza pandemic

According to the latest agreed definitions of interpandemic period published by the WHO, it has been classified into six stages (WHO).

**Stage 1:** This stage of interpandemic period has ended. It is one in which a new virus has not been identified in humans and the risk posed to humans by the new virus identified in animals is still not great.

Organisation of the Epidemiologic Service with a National Influenza Laboratory enables in the interpandemic period the monitoring of epidemiologic situation, detection of a new virus in the population, and the evaluation of vaccination programme. It is assumed that immunisation with existing strains will continue during the pandemic period as well, and the delivery of vaccine and the vaccination organization is a part of the preparedness plan. It is important to implement all the other public health measures against communicable diseases, including mass immunisation against childhood diseases, immunization with the vaccine against invasive pneumococcal disease of those at increased risk, and the prevention and treatment of the chronic diseases stipulated in Croatian Health Care Measures Programme. Because its implementation is also a part of the Pandemic Influenza Preparedness Plan, it will be crucially important for the population to meet the next potential influenza pandemic optimally fit medically.

**Stage 2:** Though no new viral subtype has been identified in humans, the virus circulating in animals exhibits an increased risk of infecting humans. A preliminary new Preparatory Plan for an Influenza Pandemic in Croatia was made at this stage. It reviewed both the present operation of the epidemiologic information system and that of the National Influenza Laboratory, also envisaging improvements in laboratory operating conditions. The Laboratory has at its disposal essential diagnostic kits for the currently circulating viruses and for the avian virus H5N1. There are veterinary measures in force banning poultry and meat imports from the countries affected by avian influenza and other measures, including sanitary, implemented on farms.

**Possible epidemic (Stage 3):** Human infection with a new viral subtype (H5N1) producing 251 sick and 147 dead has broken out in Asia. Human cases of bird influenza were also registered in Egypt and Turkey (WHO. Cumulative number of confirmed human cases of avian influenza AH5N1 reported to WHO, September 2006, [www.who.int/csr/disease/avian-influenza/country/cases](http://www.who.int/csr/disease/avian-influenza/country/cases)). The majority of patients developed the illness after direct contact with sick poultry and only limited human transmission was suspected in several cases. Concerning the travellers to destinations in avian influenza-affected countries, they have received supplementary instructions on the maintenance of their health. Our Pandemic Preparation Plan was worked out in

concert with other European countries at a Luxembourg meeting organized by European Commission and the WHO Regional Office for Europe in March 2005. What Croatia plans to do is to protect its population from a potentially pandemic strain. It bases the protection on a hypothesised number of the cases recorded in previous pandemic outbreaks. Arrangements are being made with the manufacturers for medicament purchases and for the reservation of a vaccine supply against the pandemic strain. [7,8,2-15].

**Stage 4:** Characterising this stage are small clusters of the patients with limited interhuman transmission and localised spread of the disease, which assumes that the virus has not adapted well to humans yet. During stage 4, intensive surveys of individual diseases in returnees from the areas with localised disease spread will continue. The necessary laboratory diagnostic kits will also be purchased if a new virus (other than H5N1) is found to be involved. For this purpose, additional protective measures shall be prescribed for travellers visiting the areas of viral spread, including advice on avoiding these areas if this travel is not absolutely necessary. Ban on travel to affected areas or closure of borders are not considered. It is anticipated that the Pandemic Preparation Plan will be detailed on the local (county) level. Treatment of individual cases entering the country and close contacts prophylaxis with antivirals will be provided.

**Stage 5:** Although at stage five case clusters are bigger, interhuman transmission is still localised, showing the increasing virus adaptation to humans. In parallel with the continuous monitoring of the epidemiologic situation, population immunisation campaigns will be conducted using the existing circulating strains of human influenza viruses. If found that the pandemic virus in question is indeed H5N1 (vaccine expected to be licensed), vaccinating those at high risk could be performed.

**Pandemic period – stage 6:** Stage 6 is characterised by increased and continuous viral transmission. At this stage, it will be important to draw a distinction between the period prior to virus entry into country and the one when it will have been registered there. The realisation of plans depends on the type of virus (whether H5N1 or a completely new virus), the production stage of the vaccine, and the groups so far shown to be the most vulnerable in the light of the implementation of drug protection and subsequent immunisation. Parts of the plan enabling an optimum operation of the services vital to everyday life will come into force, as will the preparation and implementation of work organisation in health service that will reduce the consequences of the pandemic. It would achieve this by providing for medical examinations and treatment of the diseased, as well as for immunisation upon the vaccine becoming available. As in previous stages, the population will be informed of the particulars of the measures in progress.

The post-epidemic period will be a return to the preepidemic period. An evaluation of the work done will be made and preparations to combat the next pandemic will be planned.

## CONCLUSION

Good organisation of the Epidemiologic Service with a National Influenza Laboratory enables in the interpandemic period – as in the case of a pandemic – the monitoring of epidemiologic situation, detection of a new virus in the population, and the prompt taking of measures for reducing the harm inflicted by the potential pandemic. Another contributing factor to this is the high percentage of vaccinated in the interpandemic period in the country, and it is one that keeps rising. It is assumed that immunisation with existing strains will continue during the pandemic period as well. Actually, the size of the pandemic would depend not only on the properties of the new virus, but also on collective immunity to the viruses having circulated in the past, as well as for those carrying some of the surface antigens in current circulation. Rapid discovery of the pandemic strain, and vaccine production would modify the pandemic, and so would all the other measures applied during the period before the pandemic vaccine becomes available. It is important to implement all the other public health measures against communicable diseases, including mass immunisation against childhood diseases, immunization of those with high risk of invasive pneumococcal infection, and the prevention and treatment of the chronic diseases stipulated in the Croatian Health Care Measures Programme. Because its implementation is also a part of the Antipandemic Preparation Programme, it will be crucially important for the population to meet the next potential influenza pandemic medically optimally fit.

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### Sažetak

Nadzor nad gripom u Hrvatskoj zasniva se na prijavi oboljenja/smrti od zaraznih bolesti o kojima se unutar 24 sata obavještava (tijekom sezone influence tjedno se dostavljaju kumulativna izvješća) Služba za epidemiologiju Hrvatskog zavoda za javno zdravstvo. Provodi se epidemiološki izvid svakog pojedinog grupiranja, a uzorci se šalju Nacionalnom laboratoriju za influencu pri Hrvatskom zavodu za javno zdravstvo.

Registrirani morbiditet od influence u Hrvatskoj iznosi 191,000 slučajeva godišnje te oscilira u interpandemijskom periodu od nekoliko tisuća pa do 190,000 slučajeva godišnje. Prosječni broj prijava u posljednjih pet godina iznosi 168 na 10000 stanovnika. Prema prijavama zdravstvenih službi za sezonu 1957/58, pandemija azijske influence A/Singapur/H2N2 uzrokovala je bolest kod više od 500,000 osoba. Pandemija hongkonške influence (A/Hong Kong/H3N2) registrirana je u Hrvatskoj u sezonama 1967./68. i 1969./70. Ukupni broj prijavljenih slučajeva influence tijekom tog perioda iznosio je 582,000 osoba (14% stanovnika). Tijekom pandemije hongkonške influence morbiditet veći od 1,000/10,000 stanovnika zabilježen je u djece starosti od 7-9 godina i u osoba starijih od 20 godina. Plan pripravnosti za pandemijsku influencu zasniva se na povijesnim podacima o morbiditetu prethodnih epidemija influence u zemlji. Kratki pregled plana pripravnosti prikazan je korištenjem faza interpandemijskog i pandemijskog razdoblja u skladu s posljednjim definicijama Svjetske zdravstvene organizacije.

**Ključne riječi:** Influenca; Epidemiologija; Hrvatska; Plan pripravnosti; Pandemija