A PROPOSAL OF ACTION PLAN FOR PANDEMIC INFLUENZA CAUSED BY A NEW VIRUS VARIANT – THE NATIONAL PANDEMIC PLAN OF THE CZECH REPUBLIC (NPP-CR)

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The problem of preparedness for an influenza pandemic has been a stable subject of discussions, under the heading of Option for the Control of Influenza, at all international influenza conferences as well as meetings of European influenza organizations (EuroGeig, ESWI and EISS). The WHO Pandemic Plan has been ready since 1999, while plans of individual countries are being gradually drawn up. They will probably have to be mutually harmonized in order that really effective coordination in the dissemination of information on the spread of influenza viruses and morbidity and in the anti-epidemic measures to be taken, can be attained.

Below, we present to the international professional public the action plan to be applied in the Czech republic (CR) when the next influenza pandemic, caused by a novel (shift) variant of the virus, reaches the CR.

BRIEF OUTLINE OF BACKGROUND KNOWLEDGE

Although epidemics and pandemics of influenza were familiar way back in the remote past (Paterson, 1986), the influenza A virus was only identified, both in man and animals, in the 20th century. Migrating water fowl have been shown to harbour the basic gene fund, which gives rise to new virus variants that then spread to and among different mammals and fowls in nature and further on to different domesticated species. As shift variants, the conditions for whose development and initial spread are not yet understood, they are a major cause of pandemics among the human population (Webster, 1998). Association with an animal (avian) source has been demonstrated for the shifted viruses involved in the so-called Spanish (1918), Asian (1957) and Hong Kong (1968) pandemics (Taubenberger et al., 1997; Scholtissek et al., 1978; Tůmová and Pereira, 1965; Webster et al., 1975). In its pandemic form, influenza may be considered a zoonosis.

During the years 1974–1984, series of well-documented influenza cases developed in humans after direct contact with infected pigs in different states of the USA. In 1986–1999 more cases of influenza – frequently fatal – were reported in limited numbers of people in various European countries, USA, and China, with the agent most often being an avian virus; none of these diseases spread any further. Interestingly, analysis of the circumstances of development of two of the local outbreaks due to A/H_5N_1 and H_9N_2 avian strains in humans in 1997 and 1999, respectively (jointly 23 cases of illness, 6 deaths),

disclosed (Eick, 2000) that the H_5N_1 virus had been present among poultry-farm workers already before 1997 and still persisted in the form of latent infection in wild birds, poultry and pigs (Claas et al., 1994; Guan et al., 2000). Any further developments in the activity of these subtypes cannot be foreseen, but they do represent a lasting future risk by their evident capacity to infect mammals including man. A similar potential risk is presented by many other virus subtypes that occur in the diverse fauna of these overpopulated areas.

There certainly is the danger of a new shift variant pathogenic for man emerging: the many-milliard population of migrant water-fowl harbour 19 genes encoding antigens that man has never encountered. However, one cannot foretell the time of appearance of the virus, its characteristics, in particular the type of its pathogenicity and virulence for man, and one can only speculate about the place where this is likely to happen (Shortridge et al., 1982). The experience of the 20th century points to central and southeast China. Nevertheless, first human infections by influenza virus occur in different parts of the world, Europe not excluded. In this light, a global influenza surveillance programme and preparedness for a potential pandemic obviously do not lack rationale.

Any human population devoid of antibodies against a new shift variant, which usually displays extraordinary pathogenicity and virulence, can only counteract an invasion by such a varient, and its consequences, by deploying a system of measures, prepared in advance, that will guarantee rapid pathogen identification and ready availability of chemoprophylaxis and specific therapy. International collaboration within the frame of an influenza surveillance programme and early dissemination of information are the first and essential conditions of implementation of such measures.

This is confirmed by the 1997 experience in Hong Kong where, under WHO guidance and for the first time, there was early implementation of a series of anti-epidemic measures, which eventually prevented development of new cases and very probably stopped the spread of the disease in minimally the local population. This has imparted impetus to the demand that plans for pandemic influenza be prepared well in advance at levels of both the WHO and individual countries.

CHARACTERISTICS OF THE NATIONAL PANDEMIC PLAN

The plan presented below starts from the WHO document (WHO, 2000) wherein the WHO sets out the actions it plans to take in the event of emergence and pandemic spread of a new shift variant of influenza virus. The WHO document also appeals to the health authorities of member countries to draw up their own National Pandemic Plans (NPP) so that measures might be taken to limit the health and socioeconomic consequences of the spread of the new shifted virus.

The first reading of the NPP-CR was prepared by the authors of this text on the basis of findings from the 1957 and 1968 pandemics (Fedová et al., 1969; Strnad et al., 1976) and was submitted to the Ministry of Health of the Czech Republic (MH CR) in November 2000. It then passed through commentation at professional medical institutions, with a focus on clinical, epidemiological and virological-diagnostic aspects, and in its final form was accepted by the State Defence Council of CR in June 2001.

Table 1. *NPP-CR implementation procedure according to the development of the epidemiological situation*

Phase	Situation	Measures
0	Interpandemic period, usual ARI season	Routine surveillance regimen
1	Shift variant appears outside Europe	NPP-WG convened, institutions and media informed
2	Increasing numbers of infections in country of variant origin, interhuman transmission confirmed, characteristics of human pathogen confirmed	Organization activities (by MH CR, state authorities, med. inst., media), verification of virol. lab. preparedness
3 a)	First cases outside the focus and country of origin	a) Enhanced activity of epidemiologists
b)	Shift variant reported in European countries	b) enhanced activity of virol. labs.
		c) public activated through media
4	Onset of 1st epid. wave in Europe Local outbreaks in CR	Start of prophylaxis in risk groups (vaccination, chemoprophylaxis)
5 a)	Epidemic starts and spreads in CR	Chemoprophylaxis continues, other antiepidemic measures introduced
b)	Nationwide epidemic	
7 a)	Postepidemic period - aftermath of 1st wave Monitoring of sporadic cases	End of chemoprophylaxis, Vaccination of uninfected persons Analysis of 1st-wave epid. situation
b)	Preparations for 2nd epidemic wave	Analysis of isolates Preparation of diagn. reagents for the new variant

The NPP-CR version presented below is in correspondence with the local conditions of CR and the contemporary possibilities of intervention. It is drawn up so as to allow easy and operative supplementation or modification in response to future developments in scientific research or the domestic socioeconomic conditions, without it being necessary to change the basic structure of the plan as outlined in Table 1 and detailed out below in the text.

Adjoined to the NPP-CR (but not included in this issue) are Methodical Instructions for clinical, virological and epidemiological facilities, with special indications for action during a pandemic.

The actions described below will be directed and coordinated by a Working Group of nine specialists, who will be in consultative contact with six other professional medical and civil institutions.

SURVEILLANCE PROGRAMME AND INFORMATION LINKS

In CR, the national-level influenza surveillance programme is mediated by the National Influenza Centre (NIC) at the National Institute of Public Health (NIPH), Prague, the Centre for Epidemiological Data Analysis at NIPH, and by regional epidemiology departments and 16 virology laboratories. Information on the epidemiological situation in acute respiratory infections (ARI) including influenza in CR is regularly supplied to the WHO world-wide FLUNET system and the European Influenza Surveillance Scheme (EISS) QUADLOGIC system by NIC, which is responsible for the maintenance of these international contacts (Tůmová, 1996).

There is mutual information exchange between the Ministry of Health of CR (MH-CR) and the WHO. The NIC is directly involved in the activities of EISS and ESWI (European Scientific Working Group on Influenza). The National Institute for Drug Control, Prague, maintains direct communication with the Committee for Proprietary Medicinal Products (CPMP) and the National Institute of Biological Standards and Control (NIBSC). Thus, exchange of topical information and its further transmission to the other participants in NPP-CR is guaranteed.

Furthermore, mutual information exchange between CR and other European countries will be possible through direct communication with the following NPP Working Group members:

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(Will be confirmed/updated in the event of a pandemic.)

WORKING GROUP FOR THE PREPARATION AND IMPLEMENTATION OF THE NATIONAL PANDEMIC PLAN (NPP-WG)

The NPP-WG was set up in April 2001, but its role will vary depending on the global and domestic epidemiological situation. As soon as the appearance of a new virus variant and its potential inter-human transmission is reported, the NPP-WG will begin functioning according to the scheme set down by the NPP-CR and the actual epidemiological situation (see Table 1).

The NPP-WG was established by the Minister of Health of CR. Directly after its nomination and the approval of the NPP-CR proposal at it its constituent meeting, the NPP-WG held its first plenary session, where further procedure in the finalization of the NPP-CR and speçification of the WG individual members' responsibilities were agreed. The group consists of a fixed number of permanent members and several expert consultants for occasional resolution of specific situations. The General Health and Sanitation Inspector is the WG's Chairman, he nominates its members and convenes and moderates its meetings.

The NPP-WG has informed WHO about the present stage of NPP preparations and has stated the key points of the plan. The manner of mutual communication in critical situations will be specified, unless it turns out to be self-evident from the internet reports on the FLUNET and QUADLOGIC, where the NIC enters weekly epidemiological and virological surveillance data.

NPP-WG STAFF

Permanent Members

- Chairman: General Health and Sanitation Inspector of CR
- Deputy Chairman (and Speaker): Chairman of the General Health and Sanitation Inspector's Consultative Panel for Epidemiology
- Secretary: Executive, Sanitation and Epidemiology Dpt., MH-CR
- Head, NIC, National Institute for Public Health (NIPH)
- Head, Centre for Epidemiological Data Analysis, NIPH
- ESWI Member (Prague Institute of Hygiene)
- Representative of Security and Emergency Management Dpt., MH-CR
- Army Epidemiologist
- Health and Sanitation Officer, Ministry of Interior of CR

- Representative, National Health Care Dpt., MH CR
- Representative, Dpt. of Pharmaceutics and Drug Control, MH-CR
- Representative, Dpt. of Finance, MH-CR
- Representative, Health Insurance Development Dpt.
- Representative, Association of Health Insurance Companies
- Representative, General Health Insurance Company of CR

Regional Epidemiologists

Consultants

- Representative, NIPH
- Representative, Czech Pharmaceutical Chamber
- Representative of general practitioners and hospitals
- Representative, Association of Drug Importers
- Representative, Veterinary Service and Research
- Representative of voluntary organization (Czech Red Cross, possibly others)

NPP-WG ACTIVITIES, HITHERTO AND NEAR-FUTURE

1. The WG has prepared a draft of its statutes
2. It has proposed a "final version" of the NPP-CR, including a governmental decree providing for NPP implementation
3. The NPP-WG has drafted MH-CR Methodical Guidelines for diagnosis, therapy and antiepidemic measures for the event that a new shift variant of influenza virus appears
4. The NPP-WG will ensure availability of a realistic number of vaccine and prophylactic-drug doses for risk groups and will draft a document defining risk groups (including professional) for priority vaccination and chemoprophylaxis
5. The WG will prepare materials substatiating additional governmental financial support for NPP realization
6. Will prepare guidelines for communication with the public and mass media
7. Will propose guidelines for communication with neighbouring countries and WHO
8. The MH CR National Health Care Department will set up a system of monitoring the hospital bed capacity in CR

IMPLEMENTATION OF THE NPP-CR AT DIFFERENT PHASES OF DEVELOPMENT OF THE EPIDEMIOLOGICAL SITUATION

Definition of Pandemic Situation

A. The risk of a pandemic is declared by MH-CR if:

1. A new shift variant of influenza virus – i.e. a virus with a new antigen (hemagglutinin and/or neuraminidase) or properties that may lead to its rapid spread – has been isolated.
2. A series of human influenza cases due to this virus have been confirmed in the locality of its emergence and other places in the region, and inter-human transmission of the infection has been established.
3. Antibodies against the agent have not been detected in the population.
4. The virus spreads to neighbouring countries.

B. The onset of a pandemic will be declared by the WHO and will be communicated to national health authorities and institutions through the internet, fax, the Weekly Epidemiological Records, and possibly through other channels.

C. When a pandemic is declared, the NPP-CR will be launched phase by phase (see Table 1).

D. Onset of the first epidemic wave of the pandemic on CR territory will be announced by the General Health and Sanitation Inspector on the basis of data of the NIC and Centre for Epidemiological Data Analysis

The phases:

0 – Interpandemic period

1 – Appearance of a new shift variant

2 – Multiple influenza cases in the focus and country of origin of the new virus

3 – a) The shift variant identified outside the country of its origin

b) Sporadic cases in Europe

4 – Onset of first epidemic wave of the pandemic in Europe – local incidence in CR

5 – a) Onset of first epidemic wave of the pandemic in Europe – local outbreaks in CR

b) Nationwide epidemic

6 – a) Postepidemic period – the aftermath of the first epidemic wave

b) Preparations for the second epidemic wave due to the new shift variant

Phase 0. Interpandemic Period

1. Influenza surveillance programmes are run under routine regimens both at national and international levels.

a) Epidemiological surveillance in CR is carried out by the NIPH, Regional Hygiene Institutes, and NIC. It comprises:

- Weekly collection and analysis of data on morbidity and complications
- The issue of weekly reports

b) Virological surveillance in CR is carried out by NIC (and other virology laboratories) and includes:

- Classical, rapid and express diagnosis
- Antiviral drug resistance testing (NIC)
- Preparation of ELISETS and diagnostics for 18 virology laboratories
- Maintenance of connection with FLUNET and QUADLOGIC
- Selective and targeted serological surveys
- Dissemination of topical information on ARD etiology

These activities are set out in detail in Methodical Guidelines for Surveillance of Influenza and Other Respiratory Diseases during a Normal ARI Season (Directive of MH CR).

2. The following provisions will be made in advance of any critical situation:

a) Arrangements with vaccine importers, in the form of contract on future contract, to supply adequate stocks of shift-variant monovaccine doses for the health service to cover risk groups and the normal population.

b) Specification of groups for priority vaccination in the event of a pandemic.

3. The following additional provisions will be made:

a) In the agreement with importers (see 2.a above), the delivery of adequate supply of registered antiviral drugs for the prophylaxis and therapy of children and adults will be stipulated.

b) The regimen of prophylactic administration of antiviral drugs (to avoid danger of resistance development) will have to be set out in special methodical guidelines issued by the MH CR.

c) The state of voluntary organizations (Czech Red Cross etc.) and their willingness to help in the event of a critical situation will have to be ascertained.

Phase 1. Appearance of a Shift Variant with Novel HA or NA Outside CR

1. Chairman of NPP-WG activates the group

2. Routine surveillance continues (epidemiology and virology)

3. NPP-WG secures monitoring of FLUNET and EISS news

4. NPP-WG informs health institutions and relevant media about the situation

Phase 2. Multiple Influenza Cases in the Focus and Country of Origin of the New Virus

1. Routine surveillance continues. NIC focuses on diagnosis of the disease occurring in the country of origin of the new variant, monitors EISS (QUADLOGIC) data.

2. The MH CR daily monitors FLUNET news and informs health institutions and media of everything relevant.

3. NPP-WG supervises overall preparedness (chemoprophylactic drug stocks, monovaccine availability, etc.).

4. NPP-WG evaluates data notified and other epidemiological information on CR and Europe including reports from army epidemiologists.

5. Regional Hygiene Institutes begin sampling of ARI cases in all age categories and regions for virus isolation, regardless of the epidemiological situation.

Phase 3. The Shift Variant Identified Outside the Country of its Origin – Sporadic Infections in Europe

1. Surveillance in CR is intensified in both of its components (epidemiological and virological).

2. There is enhanced watch for and attention to:

- Sudden increase in ARI morbidity at unusual season,
- ARI outbreaks,
- ARI cases with unusually serious course,
- Illness in persons coming from abroad,
- Increased purchase of antipyretics at pharmacies and rise in frequency of visits by First Aid Medical Service members.

3. Virological investigation of ARI cases and all deaths with a suspect postmortem finding is intensified.

4. NPP-WG convenes a meeting of its permanent members plus regional epidemiologists.

5. NIC continues to monitor FLUNET and EISS daily news, informs the NPP-WG.

6. NPP-WG Deputy Chairman, in cooperation with the MH CR Press Department, informs the public about the situation on TV and in the press.

7. NPP-WG ascertains the bed capacity in case of rise of necessary hospitalization rates.

8. NPP-WG updates provisions for distribution of monovaccine (if available) and antiviral drugs.

9. Vaccination of medical workers and other professionally exposed, socially important groups begins.

10. NIC applies for the new shift variant to prepare formolized antigen for serological diagnosis and for preparation of diagnostic sera; if necessary, NIC will secure the purchase of diagnostic reagents abroad.

Phase 4. Onset of First Epidemic Wave of the Pandemic in Multiple European Countries – Local Incidence in CR

1. Epidemiologists and virologists intensify activity, which includes: reports on morbidity, daily notification of positive influenza cases, notification of complications and deaths, District Hygiene Institutes start daily reporting on First Aid Medical Service activities and monitoring of antipyretic purchase rates at pharmacies.

2. Virology laboratories promptly submit virus isolates from suspect cases to NIC for identification.

3. NIC disseminates information on findings in CR through both internet systems; monitors the incoming information on epidemiological developments in Europe, informs the NPP-WG.

4. In line with guidelines, antiviral drugs are administered prophylactically to all nonvaccinated groups at risk (due to professional exposure or state of health).

5. NPP-WG holds meetings, depending on the immediate set-up, and resolves difficult situations: it analyzes the immediate situation and decides about further procedure.

6. NPP-WG verifies the steady run of vaccination and decides about additional initiation, or withdrawal, of antiepidemic measures.

7. NPP-WG informs the public health institutions, and through the Minister of Health the Government of CR, about developments in the epidemiological situation.

8. The media are informed regularly.

Phase 5. Onset of First Epidemic Wave on CR Territory – Local Outbreaks and Nationwide Epidemic

1. Surveillance activities continue with reports on morbidity and complications, the focus being on the numbers of cases demonstrably due to the new virus variant by locality.

2. a) NIC identifies strains isolated and determines their susceptibility to the antiviral drugs in use.

b) Other laboratories proceed according to the methodical guidelines of MH CR.

3. The Association of Importers of Pharmaceuticals together with the Pharmaceutics Dept. of MH CR furnish information on the stocks of antiviral drugs and nonspecific anti-influenza therapeutics, as well as on their sale.

4. MH CR advise general and paediatric practitioners to modify their service regimens (restrict patients' attendance in surgeries, increase doctors' visits to patients' homes).

5. NPP-WG requests voluntary organizations to undertake care of elderly patients (fetch their medicines, do their shopping for them, etc.) during the epidemic, in so far as these services are not provided for them otherwise.

6. Together with the institutions concerned and consultant, the NPP-WG organizes antiepidemic actions.

7. Depending on the gravity of the situation, the General Health and Sanitation Inspector may prohibit visits at in-patient wards and impose a limitation on mass gatherings.

8. Chemoprophylaxis continues in indicated situations.

9. All antiepidemic measures are implemented under article 6, para. 1 and 2, of Act No. 258/2000, Law Gazette.

Phase 6. Postepidemic Period

a) The aftermath of the first epidemic wave, analysis of the epidemiological situation.
b) Preparations for the second epidemic wave due to the new variant.

1. Surveillance continues, a preliminary analysis of the epidemic-associated morbidity, complications, mortality and virological findings is made.

2. NPP-WG requests the Statistical Bureau to submit its data on morbidity related to predetermined diagnoses.

3. Prophylactic administration of antiviral drugs is stopped.

4. One week after the NPP-WG-declared end of the first epidemic wave, vaccination with monovaccine, if available, of further risk and professional groups is initiated.

5. Persons in special risk, including persons above 60, are revaccinated with a second vaccine dose, in so far as they did not contract the infection in the first wave.

6. NPP-WG will evaluate the first wave period and prepare a report in which the state of preparedness and the antiepidemic measures taken will be assessed. This report will be submitted to the MH CR and the Government of CR and the public will be informed about it through the media (the Czech press agency ČTK, the TV).

7. NPP-WG will continue its activities through the second epidemic wave of the pandemic.

8. Phase 0, point 1 is reinstated.

Period between the First and the Second Pandemic Wave

Should the epidemiological situation be similar to that of the 1957 and 1968 pandemics, the second wave could be expected in 5–8 months, but it may very likely come earlier. Presumably the demands on prompt implementation of the general and the special antiepidemic measures will be higher this time; a much more consistent incorporation of the therapeutic and preventive components of the health service will be a necessity. It will be necessary to start from the premise, resting on years of experience, that the virus may after several months' circulation be modified to a highly pathogenic, virulent, and very possibly toxic agent. In view of this, a more serious course of the disease, frequent complications, and death-rate excesses are highly probable.

General Measures:

1. Notification of morbidity, complications, and mortality should be extended over the whole period between the 1st and 2nd epidemic waves.

2. Influenza etiology of ARI cases should be actively looked for and virologically determined by agent isolation and seroconversion.

3. The virus should be promptly characterized and tested for susceptibility to the antiviral drugs available.

4. Antiepidemic measures applicable in affected groups will be retained in order to limit both internal and external spread of the agent.

Special Measures:

1. A strategy for continued vaccination (with mono- and trivaccine) should be drawn up.

2. Cooperation rules for hospitalization of complicated cases should be set down.

3. Deaths should be notified and influenza etiology confirmed in postmortem samples.

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