Hungarian National plan for the pandemic preparedness to influenza
(Interim working document)

Gy. Takatsy, I. Dömök, I. Jankovics, Gy. Berencsi, B.Johan; National Center for Epidemiology, Budapest, Hungary

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1. Professional background, justification

Influenza is the most important viral infectious disease returning regularly. In case of a medium degree epidemic, 20-40 % of the population can be affected, and considering the epidemiological experiences of the last thirty years, in Hungary the number of complications and lethal cases may be high. The public health authorities in Hungary provide free-of-charge vaccine supply every year for the risk population since many decades. Recently the coverage has riched about 10 % of the total population.

The emergence of a pandemic influenza virus, is one of the greatest challenge of the world population. An the planning and organisation of the preventive activities is one of the principal responsibilities of Authorities and Organizations working in public health and medicine. In case of a pandemic epidemiology is facing practically a new virus because of the profound structural changes of the surface of the virus.

In this case it is recommended to provide several times higher level of the preventive vaccination, than that usual in interpandemic years in order to prevent the expectable increased number of complicated illensses. The vaccination of the professionals required for the maintenance of the of the everyday functioning of the country will be also necessary. This amount of the killed whole virus vaccine will be more than one million of doses in a country of the size of Hungary.

During the last 5 years the appearence of 4 new subtypes of influenza A virus has been reported (H1N2; H5N1; H9N2 and H7N7). There is, however, no possible way of prediction when a new subtype will emerge in nature, which will be adapted to the neuraminic acid receptors of the human mucous membranes and beginning pandemic spread.

The pandemic preparednes, however, may be facilitated by the new drugs developed recently inhibiting neuraminidase enzymes of all influenza viruses tested up to now. Their problem is the relatively short shelf life. The experts suggest, that the tablet forms may be stored for longer periodes under appropriate conditions.

In May 2003 (St. Petersburg - WHO - CDC - NATO Workshop) it has been predicted by the Association of Vaccine manufacturers, that about 300 million doses of vaccine can be prepared within the first 6 months following the apperence the new pandemic strain. The Hungarian preparedness plan therfore is based on the "cold-capacity" of the Hungarian Manufacturer with GMP accreditation.

The WHO recommendations suggest the provision of several times higher amount of vaccine doses than that of the interpandemic demand. The national Health and Public Health Authorities are nominated as organizations being responsible for the fulfillment of the recommendations. The recommendations also suggest, that the Ministry of Health and the local vaccine manufacturers has to agree on the conditions and the quantity of new vaccine guaranteed in an emergency (pandemic) situation.

The pandemic preparednes involves good timing and successful preparation after the onset of a pandemic. This will be a distinguished epidemiological interest of the country therefore it will require the coordinated action of the governmental organizations of epidemiological, medical and public health responsibilities.

In case of a pandemic, without the adequate supply and quality of specific vaccine it cannot be probably purchased in due time under acceptable financial conditions by the Ministery of Health from the free market. This case Ministry of Health cannot accomplish its task and responsibility laid down in the Hungarian Statute, corresponding lows and epidemological regulations.

If the competent governmental organizations didnot care for the inspection and operation of excess manufacturing capacities capable to produce the required excess amount of specific vaccine in comparison to the interpandemic demand it would create danger for masses of citizens (including also the population at high risk). In addition, functional disturbances would evolve in the work of persons, organizations and authorities, fulfilling basic tasks in health care, authorities, civil and public services (i.e. police, fire-service, army etc.).

The special technical-technological requirements regarding the quality and functioning of "cold-capacity" are the following (as recommended by the responsible health- and public health supervisor organizations:

1.) The production in a pandemic emergency situation, and the distribution of the vaccine for the population is the race of public health with time. Many operations (isolation of the new subtype, mass production, quality control of the product, vaccination, two weeks time for the development of immunity of vaccinees, and the continuous surveillance and epidemiological services) should have to preceede the onset of the pandemy in the country.

- mass production, and the quality-control performed by the manufacturer

- product release by authorities
- distribution of the vaccine and vaccination
- development of specific immunity within two weeks following vaccination (according to recent publications a two-dose schedule may be required in order to increase resistance against a new subtype)
- operative function of surveillance system and that of diagnostic centres.

2.) The beginning of the pandemic mass production using the "cold-capacity of the manufacturer" has to be officially recommended and financially supported by the Govermental health Authorities upon the distribution of the pandemic strain by the International Reference Laboratories of WHO. The production itself requires coordinated daily cooperation of the manufacturer and the National Control Authority. The co-operation may achieve the simultaneous control of the technological part-processes, the simultaneous in-process control, and a parallel collective consultative control and evaluation of product release.

3.) To ensure the immediate and safe vaccine supply of the population, all factors has to be excluded which might hinder or delay the realisation of pandemic production. Such factors may be:
- delaying or even preventing the import of materials from foreign manufacturers;
- strikes retarding air and other kind of transportation,
- blocking of the boarders;
- liberation of export-import regulations (tender regulations) for goods associated with pandemic preparedness and any influenza vaccine production or control;
- delay because of panic incidents;
- special handling of natural catastrophs;
- special regulations for custom administration;
- preventive measures of other countries, which may prolong external authority controls;
- etc.

These factors may create unpredictable conditions, which cannot be overcome or prevented and sanctionated by civil law contracts and may hinder safe pandemic preventive treatment and supply of the population in spite of carefully prepared contracts and well arranged import services.

It may happen, that one-day delay of arrival of a sample, or not accomplishing of a local inspection may endanger the vaccination of 70 000 persons. Three to four days' delay may retard the vaccination and even immunisation of about quarter-million persons.

4.) The Health Management can safely direct and fulfil the professional requirements and controls at high degree of efficiency if the "cold capacity" is found in factories, working within Hungary. This plant may be inspected any time, requested data are available any time and all problems of production and control can be solved immediately in co-operation with the manufacturer.

5.) Beyond the above details the following special factors are required as basic conditions of the "cold capacity":

- Working ability: it has to be based on a continually working manufacturing facility, which is possessing the material, technical and personal supplies in order to increase the

production capacity three fold (i.e. to the production of four million doses of influenza vaccine).

- Continuous preparednes, and possibility of the beginning of the pandemic production at any time, because the date of emergency manufacturing periode cannot be predicted, but the release of the required vaccine subtype has to be guaranteed.

Since the government does not posses production facitlity for influenza vaccine production and the availebility of the provision of influenza vaccine is uncertain from the free market, it has been decided due to qualified epidemiological interest to work out the national pandemic preparedness plan based on the cold-capacity of the GMP accredited private manufacturer in Pilisborosjenoe.

II. Aims of the preparedness plan

The aim of the preparedness plan is,

1. To recognize the appearance of the pandemic causative strain as soon as possible (in case it will appeare in Eastern Europe);
2. To create the conditions of the pandemic vaccine production (increased output of fertilised eggs, virus production, etc.);
3. To define conditions, which enable and promote the accelerated quality control, approval and release of the produced vaccine batches (in co-operation with the authorities);
4. To create the organizational conditions of the vaccine distribution and vaccinations simultaneously providing excess financial coverage of the vaccine utilization;
5. To coordinate the local tasks, coordinating the international preventive and surveillance plans;
6. To make aware responsible authorities, institutions, diagnostic and manufacturing laboratories including all the experts concerned that they are bearing both personal and social responsibilities in the implementation of the "pandemic preparedness plan" including specific sub-projects;
7. To ensure the integrated communication strategy for managing the expectable atmosphere of panic among the population.

III. Tasks defined on the basis of the preparednes plan

1. One can consider an influenza A virus subtype being a pandemic starin, which has acquired at least one or sometimes two completely new surface proteins (haemagglutinin and neuraminidase).

   1.1. The first duty of the Hungarian virologists is follow the scientific literature, and continue international co-operation in the fields of laboratory diagnostic and epidemiology. This duty concerns primarily the co-workers of the Influenza Reference Laboratory of the "B. Johan" National Center for Epidemiology.

   1.2. The whole population of the world is susceptible to the pandemic influenza A virus strain. Nobody can possess neither residual humoral immunity from previous infections nor from previous vaccinations unless one of the surface glycoproteins remained unaltered.

Therefore the new vaccine against the new pandemic strain has to be put at the disposal of the countries as early as possible.

At the moment in Hungary the only laboratory producing influenza vaccine conforming to international standards is the manufacturer OMNINVEST (Vaccine Manufacturing and Research Development Company), located in Pilisborosjenoe. Its pandemic preparedness programme is shown in Table I.

The precondition of ensuring the pandemic increase of the production capacity is the sustained activity of the experienced expert-staff at the production unit including the accredited equipment continuously held ready for production. Thus as part of the pandemic plan the Hungarian production of the annually utilized vaccine quantity also in the meantime has to be ensured.

1.3 Alternative preventive measures are possible (pharmaceutical prevention and epidemiological provisions), but previous experiences show that Amantadin and Rimantadin are not effective in prevention. The possible role of neuraminidase inhibitors seem to be more promising. Epidemiological quarantine can be realised only in smaller communities (hospital departments) and these can be temporarily protected from the infection.

1.4 In order to detect the appearence of the new pandemic strain into Hungary the annually (between October and March) reorganized surveillance system is suitable. This surveillance is based on the cooperation of voluntarily involved general practitioners and on the Regional and Backup Intitutions of National Public Health and Medical Officer Service (NPHMOS). This surveillance system has been completed since 2002 by the laboratory surveillance of ILI and since 2003 by the surveillance for SARS Coronavirus. The latter has been a training for the recognition of the next pandemic influenza strain.

1.4.1.) The diagnsotic procedure of the laboratory surveillance has been modified in 2002, too. In addition to the direct detection of the etiologic agents using moniclonal antibodies samples are also processed for the detection of genomes of adenoviruses, parainfluenza viruses, RSV completed by SARS Coronavirus-spcific RT-PCR in 2003.

Cultivation of influenzavirus strains is national and also international interest, because it is the precondition of establishing epidemiological preventive measures, and the strains isolated from the epidemics have to be transmitted to WHO every year. This is the only way to follow up and compare the antigenic changes, and to make the recommendation for vaccines in the next year.

Establishing the financial cover of the surveillance system from the central budget is an important condition of both the pandemic preparedness plan.

1.4.2.) There is a central project in preparation for the technical and methodological development of the laboratory background of the diagnostic and molecular epidemiological surveillance system. Rapid diagnostic tests and real-time procedures will be introduced in the laboratories of the NPHMOS. Unfortunately the use of rapid diagnostic tests cannot be used by general practitioners and ambulances because of financial reasons.

2.) The first step in the local vaccine production has to be made at the National Reference Laboratory of Virology Division of the National Center for Epidemiology. The preparation of the seed virus from the recommended pandemic isolate distributed by the WHO Reference laboratory as soon as possible.

2.1. If the pandemic virus strain arrives in the usual vaccine manufacturing period, the production process will be immadiately stopped. The new seed virus of the pandemic strain will be introduced, and the "cold-capacity" will be stepwise activated increasing the volume of the product. The amount of the available pandemic vaccine will be increased, since the Hungarian vaccine is:

- Whole virus vaccine,
- Adjuvated vaccine,
- And instead of the trivalent composition the pandemic vaccine will be a monovalent one according to the Up-date distributed by Dr. Klaus Stöhr on the 1st of October, 2003.

In case the pandemic virus arrives during the interuption of the vaccine manufacturing periode the problem of the reinitiation of the production is more complex. The firms supplying fertilised eggs has to increase production first, and the production of the new subtype can be continued only with some delay. The increased mass of fertilised eggs obtained from Leghorn poultry farms with white shell may cause an additional problem.
It may occur, that other Salmonella- and Mycoplasma-free poultry eggs have to be transiently used for the increased manufacturing.

2.2. The production capacity has to be increased, because about 3-4 million inhabitants has to be vaccinated over the usual annual demand. The demand of pandemic vaccine will be even higher when two shots will be recommended by the WHO experts in order to increase specific immunity.
2.3. The national pandemic production has to be continuously supervised by the National Control Laboratory.

3.) In order to be able to distribute the pandemic vaccine as early as possible, the stepwise periodical packaging and quality control of the manufactured vaccine bulks (inactivated virus pools) will be advisable. The individual monovalent pandemic virus bulks (inactivated monovalent virus pools) will be controlled according to the Serial Numbers of the bulks. The data shown in the time table of virus vaccine production (Table I) indicate, that 9 weeks following the arrival of the pandemic strain(s) the first controlled final product can be distributed.

3.1. The periodical production and control can only be possible, if the intermediate products are simultaneously controlled by both the National Control Laboratory and the manufacturer itself.

3.2. To start the vaccinations as soon as possible, the controll authority has to take and superwise the submitted control documentations upon the completion of the in process control tests and it has to make certain examinations parallel with the manufacturers not to delay the process of vaccine distribution.

3.3. The epidemiological risk makes it reasonable to omit all usual, previously manufactured virus strains from the composition of the emergency pandemic vaccine during the manufacturing process in the year (periode) concerned.

4.) The expenses of the approximately 3-4 million excess doses of vaccine has to be covered from the govermental reserves retained in the budget for emergency and hazard situations or events. The production of the given amount of excess pandemic vaccine will take about 9-16 weeks (Table I).

4.1. The first final lot can be released on the 9. week, following the distribution of the prototype strain by WHO to the National Influenza Centres, subsequent lots come weekly thereafter. By this periodical production it is supposed that the NPHMOS can distribute about 500 000 doses to the target population every week taking into account, that a reassortant PR8-based pandemic seed virus is available. Previous experiences indicate, that this work is a very hard task for the system, but it is possible by appropriate reorganisation of the men-power.

4.2. The vaccine distribution network of pharmacies would be supplied weekly, considering the economic consequences of the epidemics. The first products, however, have to be distributed to target groups at the highest risk living with predisposing medical conditions and to health care workers in contact with them.

4.3. Although the distribution is periodical, the reports will be collected and analysed only at the end of the vaccination campaign, in order to avoid any excess work for that created by the vaccination campaign itself and by the tasks created by the pandemic itself.

5.) The media can be used to inform the population and health personnel in connection with the problems and tasks of the pandemic preparedness. In the case the pandemic influenza subtype will appear the education and professional preparations have to be accelerated, increased and the above activities have to be initiated.

IV. Summary

1. The maintenance of production-, and availability of cold-capacity, has to be maintained in Hungary, as well as the availability of regular authority control has to be continuously ensured by the anual production and distribution of the recommended amount of influenza vaccine for the risk populations free of charge in cooperation with the privat manufacturers within the country.
2. The virological surveillance has to be developed concerning the integrated education, the sampling and receipt, the use of rapid diagnostic methods, and the data processing and analysis.
3. The epidemiological surveillance has to be improved in order to analyse local epidemiological data and geographical distribution of ILI for the possible introduction of necessary epidemiological measures.
4. The teaching and health education has to be continued in interpandemic periods as well.

5. The methodology the schedule of emergency vaccine production and accelerated vaccine control has to be elaborated in detail.
6. The details of the appropriate storage and distribution of the excess amounts of pandemic vaccine supply has to be elaborated, too. The rapid distribution of the vaccine and periodical rapid vaccination according to professional rules for the populations of decreasing risk is an economical problem, since the stockpiling can be reduced by rapid vaccination.
7. Excess expenses of the emergency pandemic vaccine supply have to be reserved through the official administrative and publich health channels immediately when the pandemic subtype will be identified.
8. A communication plan will be required necessary to provide continuous exchange of reliable information both for organizations, and the people including and utilising the media.

Table I.

Time-table of the plan of pandemic vaccine manufacturing and vaccination process based on the data of the coldcapacity available in Pilisborosjenoe in Hungary.

0.day	Arrival of the new subtype of influenzavirus in the Reference Laboratory at the National Center for Epidemiology, Budapest
1.week	"Master seed" is prepared for the industrial production
2.week	Inoculation of the first 150 000 eggs
3.week	Preparation of the monovalent bulk. No. 1. Inoculation of the second 150 000 eggs
4.week	Preparation of monovalent bulk No. 2. Inoculation of the third 150 000 eggs
5.week	Preparation of the monovalent bulk No. 3. Inoculation of the fourth 150 000 eggs
6.week	Control of the monovalent bulk No. 1. is completed Formulation and filling of Final Lot No. 1. Quality control of Final Lot. No. 1 begins simultaneously with that of the National Control Laboratory Preparation of the monovalent bulk No. 4. Inoculation of the fifth 150 000 eggs
7.week	Control of monovalent bulk No. 2. is completed Formulation and filling of the Final Lot No. 2 Quality control of Final Lot. No. 2 begins simultaneously with that of the National Control Laboratory Preparation of monovalent bulk No. 5. Inoculation of the sixth 150 000 eggs
8.week	Control of monovalent bulk No. 3. Is completed Formulation and filling of the Final Lot No. 3. Quality control of Final Lot. No. 3 begins simultaneously with that of the National Control Laboratory Preparation of the monovalent bulk No. 6. Inoculation of the seventh 150 000 eggs

9.week	Administrative approval and release of the first 500 000- 700 000 doses ov vaccine. Beginning of vaccination of risk groups. Control of monovalent bulk No. 4. Is completed Formulation and filling of the Final Lot No. 4. is completed Quality control of Final Lot. No. 4 begins simultaneously with that of the National Control Laboratory Preparation of the monovalent bulk No. 7. *
10.week	Administrative approval and release of the second 500 000- 700 000 doses. 2nd round of vaccination campaign (among professionals and persons at lower risk) Control of monovalent bulk No. 5. is completed. Formulation and filling of the Final Lot No. 5. is completed Quality control of Final Lot. No. 5 begins simultaneously with that of the National Control Laboratory * and **
11.week	Official approval and administrative release of the third 500 000- 700 000 doses. 3rd round of the vaccination campaign for professionals, persons at lower risk and probaly revacination of patients at risk immunised two week earlier. Control of monovalent bulk No. 6. is completed. Formulation and filling of Final Lot No. 6 is completed Quality control of Final Lot. No. 6 begins simultaneously with that of the National Control Laboratory * and **
12.week	Administrative approval and release of the fourth 500 000- 700 000 doses. 4th round of vaccination (professionals, people at risk, revaccinations if recommended) Control of monovalent bulk No. 7. is completed. Formulation and filling of the Final Lot No. 7. is completed Quality control of Final Lot. No. 7 begins simultaneously with that of the National Control Laboratory * and **
13.week	Administrative approval and release of the fifth 500 000- 700 000 doses. 5th round of vaccination (voluntary vaccinees and professionals including risk population and revacinees) * and **
14.week	Release of the sixth 500 000- 700 000 doses. 6th round of vaccination campaign * and **
15.week	Release of the seventh 500 000- 700 000 doses. 7th round of the vaccination campaign
With this process 3,5-4,9 million persons can be vaccinated until the end of the 16.week. * in case the demand will not be reduced subsequent production cycles ** new bulks and lots can be produced if the first epidemic will not be over, or in case the vaccine has to be put at the disposal of other countries.	