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**COMMISSION WORKING PAPER**

**on Community Influenza Pandemic Preparedness and Response Planning**

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## **EXECUTIVE SUMMARY**

This working paper addresses key issues of national and EU relevance of influenza pandemic preparedness and response planning. It explains the stages of an influenza pandemic on the basis of the definitions of the World Health Organisation (WHO) and sets out the main objectives of action. Moreover, it outlines the role of the Commission and the Member States in pandemic preparedness planning and defines key actions at pre-determined phases and levels in the main areas of management and co-ordination, surveillance, prevention, mitigation and response, communication, civil protection and research. Particular reference is made to animal health legislation and actions that aim to prevent and control influenza in animals, in particular avian influenza, which can have a major role in the emergence and impact potential of human influenza.

The paper has been prepared following extensive consultations on pandemic influenza with the members of the Communicable Disease Surveillance and Response Network Committee hereinafter referred to as “Network Committee”, established under Decision 2119/98/EC of the European Parliament and Council<sup>1</sup> setting up a network for the epidemiological surveillance and control of communicable diseases in the Community, and an ad hoc group on influenza set up to advise the Commission services. The WHO and the European Medicines Evaluation Agency (EMA) also took part in these consultations. The working paper was reviewed at a meeting in October 2003 of the Public Health Preparedness and Response Planning Group (PRPG), which was set up to advise the Commission on all matters concerning public health emergencies.

The paper should serve as a launchpad for a debate on co-ordinating preparedness against influenza and on recommendations that can be made in this respect. This will be done in parallel with the development of a general plan for public health emergencies that the Health Ministers requested following the SARS outbreak, and will provide the basis for a specific component of this general plan in order to fine-tune measures in respect of an influenza pandemic.

The proposed plan sets out a considerable agenda for action that will have to meet with the agreement of and receive the support of the Member States. Certain actions, such as the establishment of the PRPG, have already been implemented. Most, however, will have to be undertaken once there is acknowledgement of the need and usefulness of the plan for the health authorities of the Member States. The plan would then have to be put in place gradually. A significant number of the actions under the preparedness plan would have to be implemented at the time of an actual influenza outbreak that risks developing into a pandemic. The proposed European Centre for Disease Prevention and Control (ECDC), once established, will play a key role in this as well as in providing further advice on influenza outbreaks.

Matters covered by this paper will be regularly reviewed and reports to the Council will be made on the basis of the information to be sought from the Member States Competent Authorities (CAs).

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<sup>1</sup> OJ L 268, 3.10.1998, p.1

## 1. INTRODUCTION

Influenza pandemics are likely to have severe public health and economic implications. In 1918, the pandemic, so-called “Spanish flu” due to the death of a member of the Spanish Royal Family and intense reporting by the Spanish media, caused about 20 million deaths worldwide. On average pandemics causing high morbidity and mortality have occurred every 25 years during the last century, whereas the last pandemic took place more than 30 years ago.

An influenza pandemic may be described as an epidemiological event characterised by the global circulation of a new virus sub-type in humans with no or little immunity, or of a virus causing morbidity and mortality that significantly exceed average seasonal epidemic rates.

Since influenza outbreaks occur regularly every year, it is extremely important to be able to judge whether they could reach severe epidemic proportions and eventually develop into pandemics. This calls for appropriate vigilance and for microbiological and epidemiological surveillance systems that can provide accurate predictions and timely warnings.

In preparation for influenza pandemics, certain Member States have developed systems of national influenza pandemic planning based on the WHO guidelines adopted in 1999. Because of the characteristics of pandemics, however, and the special features of the European Union area in which people, animals and products circulate freely, the question of the need for Community action to co-ordinate preparedness and response in the EU had become critical.

To address it, the Commission organised a conference on influenza pandemic preparedness planning in November 2001 in Brussels at which delegates from the Member States and accession countries, independent experts and stakeholders from Europe and overseas countries participated. The delegates recognised and agreed on the need for Community action. The conference concluded with recommendations for core actions at Community level, which form the key elements of the proposed Community Influenza Preparedness and Response Plan, hereinafter referred to as the “preparedness plan”, presented in this working paper. The preparedness plan further develops certain elements of the guidelines adopted by the WHO in 1999.

In parallel, extensive consultations on pandemic influenza were undertaken with the members of the Network Committee and with an ad hoc working group on influenza set up to advise the Commission services. The WHO and the European Medicines Evaluation Agency (EMA) have been closely associated with these consultations.

The working paper was drawn up on the basis of the aforementioned actions and considered and reviewed at a meeting in October 2003 of the PRPG. This group has been set up to advise the Commission services on matters concerning public health emergencies following the request of the Health Ministers to the Commission, in the light of the SARS outbreak, to develop a general plan for public health preparedness and response to health threats whatever their provenance.

From the animal health point of view, which is a crucial factor because of the direct links with human influenza, it should be pointed out that, in pursuance of Directive

92/40/EEC<sup>2</sup> introducing Community measures for the control of avian influenza, contingency plans for this disease have been developed, approved by the Commission and implemented by Member States CAs in the event of outbreaks.

Furthermore, in 2003, the Commission endorsed a survey on avian influenza in domestic poultry and wild birds in the Member States. First results are already available. Based on the results of this survey, the Commission intends to propose a strengthened approach to avian influenza infections, including reinforced surveillance, which also takes account of public health aspects related to prevention and disease transmission from poultry to humans. The current avian influenza in Asia, on which a series of measures have been taken, provides a further demonstration of the need for rigorous methods and practices in this area.

## **2. PRINCIPLES, OBJECTIVES AND COMPONENTS OF THE PREPAREDNESS PLAN**

Experience has shown that the ability to respond to an international threat to health is profoundly influenced by the extent to which the issues have been considered in advance and plans are in place for co-ordinated action.

Detailed guidance on national preparedness plans is contained in the WHO document 'Influenza Pandemic Plan. The Role of WHO and Guidelines for National and Regional Planning' (WHO Geneva, 1999)<sup>3</sup>. The document was taken into account for the preparation of this paper, which addresses the planning needed for the European Community to respond effectively to a potential or actual pandemic of influenza.

The purpose of the preparedness plan would be to minimise the risk of a pandemic, to ensure preparedness and to achieve a co-ordinated Community response in the event of an influenza pandemic through:

- Identification of the key components of the response.
- Identification of those activities of the Commission, the European Agency for the Evaluation of Medicinal Products (EMA) and the Member States that could facilitate and help co-ordinate countermeasures.
- Setting the Community response in the context of the wider international response through co-operation with international organisations such as the WHO.

The main objectives of the preparedness plan are:

- Facilitate a timely response.
- Contribute to reducing vulnerability of public health, particularly limiting excess morbidity/mortality.
- Help to reduce fear in the population, including healthcare professionals.

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<sup>2</sup> OJ L 167, 22.6.1992, p.1

<sup>3</sup> [http://www.who.int/csr/resources/publications/influenza/WHO\\_CDS\\_CSR\\_EDC\\_99\\_1/en/](http://www.who.int/csr/resources/publications/influenza/WHO_CDS_CSR_EDC_99_1/en/), accessed 17.11.03

- Limit disruption to normal activities as far as possible.
- Reduce potential conflicts between different national plans.

The preparedness plan put forward in this paper comprises the following components:

- A division of the influenza “cycle” into pre-defined phases and levels, which have to be recognised on the basis of agreed criteria and which act as triggers for countermeasures by the Commission and by the Member States.
- A set of key functions that need to be discharged properly if influenza pandemics are to be tackled effectively. Management and co-ordination, surveillance, prevention and intervention strategies, civil protection, communication and research are the key functions covered under the preparedness plan.
- The establishment of Community-level mechanisms to ensure that there is effective co-ordination and joined-up action at every stage of an influenza outbreak that risks developing into a pandemic:
  - Firstly, for management and co-ordination, the Community can use the mechanisms provided by Decision 2119/98/EC<sup>4</sup>, namely the adoption of Commission decisions following a positive opinion from the Network Committee for measures such as the declaration of a pandemic situation and mandatory consultation procedures, and for co-ordination of measures as provided by Commission Decision 2000/57/EC<sup>5</sup> on the early warning and response system for the prevention and control of communicable diseases. Secondly, the Commission services will be advised by the PRPG on the appropriate actions to be considered. The PRPG is composed of experts designated by the Member States and will be convened according to the guidelines set out in the preparedness plan.
  - In the context of intervention strategies, retrospective evaluation of the experience gained during serious outbreaks of communicable diseases outside the European Union has illustrated the need for a consensus on the co-ordination of international outbreak investigations. Such co-ordination is equally useful for outbreaks within the EU. In order to meet this need it is proposed that an Outbreak Assistance Team (OAT) be assembled and activated on advice from the PRPG.
  - For surveillance, appropriate mechanisms exist, namely the Communicable Disease Surveillance and Response Network and the avian influenza surveillance scheme on domestic poultry and wild birds co-ordinated by the Community Reference Laboratory for Avian Influenza. They should be complemented by a Community Network of laboratories for human influenza, because effective surveillance at Community level depends on the expertise and capacity of laboratories in the Member States to detect potentially dangerous influenza viruses in

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<sup>4</sup> OJ L 268, 3.10.1998, p.1

<sup>5</sup> OJ L 21, 26.1.2000, p.32

good time. Surveillance data should include information on strains in humans and animals, the burden of disease and vaccination coverage, effectiveness and safety.

- The encouragement of specific prevention measures. In the event of a pandemic, the swift development and distribution of new vaccines and availability of antivirals will be of utmost importance in tackling the disease. Equity of access to these medicines is a pre-requisite and, for new vaccines, timely delivered guidelines will be crucial in order to reduce the time needed for their marketing authorisation. Stockpiling of antivirals to cover the lead time needed to develop and produce new vaccines should be encouraged.

### **3. PHASES AND LEVELS**

The WHO has suggested various criteria to define phases in line with the unfolding epidemiological situation of a pandemic. In addition, the definition of levels of preparedness provides a basis for WHO to determine its response to such situations as they are assessed on the basis of the occurrence of specific events and associated risks, as indicated in the table below. The classification system used in this document is based on the WHO classification and is consistent with the criteria adopted in other areas of work at Community level, such as the marketing authorisation for medicinal products for human use and veterinary medicinal products, generic public health emergency plans and smallpox preparedness planning, which take into account the specificity of the EU. In particular, the recognition of a pandemic situation can be made in the context of Decision 2119/98/EC. For medicinal product marketing purposes, such recognition will be based either on a pronouncement of the WHO or by the Community in the framework of Decision 2119/98/EC, as laid down in Commission Regulation (EC) No 1084/2003<sup>6</sup> concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products, and in Commission Regulation (EC) No 1085/2003<sup>7</sup> concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products falling within the scope of Council Regulation (EEC) No 2309/93. The classification system used is given in the following table which sets out best and worst case scenarios for the EU and also shows the correspondence with the WHO phases and levels.

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<sup>6</sup> OJ L 159, 27.06.2003, p.1

<sup>7</sup> OJ L 159, 27.06.2003, p.24

**Table of correspondence**

EU		Criteria: origin of outbreak		WHO		Criteria
Phase	Level	Outside EU	Inside EU	Phase	Level	
0	0	No indications of any new virus type reported in humans	No indication of any new virus type reported in humans	0	0	No indications of any new virus type reported in humans
0	1	Isolation of novel subtype from a single human case	Isolation of novel subtype from a single human case	0	1	Isolation of novel sub-type from a single human case
0	2	Two or more human infections with a new subtype	Two or more human infections with a new subtype	0	2	Two or more human infections with a new subtype
0	3	Human to human transmission confirmed	Human to human transmission confirmed	0	3	Human to human transmission confirmed
1		Several outbreaks in at least one country outside EU, spread to other countries	Several outbreaks in at least one Member State, spread to other countries	1		Confirmation of onset of pandemic : several outbreaks in at least one country, spread to other countries
2	0	Regional and multi-regional epidemics: no indications of any new virus type reported in the EU	Regional and multi-regional epidemics in the EU	2		Regional and multi-regional epidemics
2	1	Regional and multi-regional epidemics: isolation of novel subtype from a single human case inside EU	Regional and multi-regional epidemics in the EU	2		Regional and multi-regional epidemics:
2	2	Regional and multi-regional epidemics: two or more human infections with a new subtype inside EU	Regional and multi-regional epidemics in the EU	2		Regional and multi-regional epidemics
2	3	Human to human transmission with new subtype confirmed inside EU	Regional and multi-regional epidemics in the EU	2		Regional and multi-regional epidemics:
2	4	Outbreaks in one or more Member States	Regional and multi-regional epidemics in the EU			
3		End of the first pandemic wave	End of the first pandemic wave	3		End of the first pandemic wave
4		Second or later waves of the pandemic	Second or later waves of the pandemic	4		Second or later waves of the pandemic
5		End of the pandemic (back to phase 0)	End of the pandemic (back to phase 0)	5		End of the pandemic (back to phase 0)

#### 4. THE COMMISSION AND THE MEMBER STATES: MAIN TASKS AND ROLE

The tasks required in each phase and at each threat level should be directed towards identifying and addressing the current impact and subsequent threat potential of the influenza outbreak in order to limit its consequences. Transition from one stage of activity to a subsequent one may, however, need to be rapid, depending on the evolution of events, and certain phases or levels may have to be leapfrogged. Plans need to be flexible to allow for this contingency. The objectives in each of the main functions to be discharged as the epidemiological situation develops are set out below.

##### 4.1. Management and co-ordination

###### 4.1.1. Main objectives

All phases and levels:

- Further develop and update the Community preparedness and response plan, emphasising the added value to the European Community;
- Ensure that national pandemic preparedness and response plans are well co-ordinated and regularly updated.

*Phase 0, level 3 and subsequent phases:*

Agree guidelines for advice to travellers, air and other transport staff likely to be occupationally exposed, health care staff and the public.

*Phase 2, levels 3 and 4 and subsequent phases:*

Co-ordinate measures to be taken by the Member States and ensure their interoperability.

###### 4.1.2. Role of the Commission and the Member States

EU added value can be achieved by improving co-ordination and communication among the Member States and with the WHO. A two-tiered structure is proposed:

###### **Public Health Preparedness and Response Planning Group (PRPG):**

The PRPG has already been established. It is modelled on its predecessor group set up under the Health Security Committee for deliberate releases of biological and chemical agents and draws on the experience gained during the SARS epidemic in the framework of the Experts Group on SARS. The tasks of the PRPG are:

- Provide advice on risk assessment.
- Recommend actions to be taken.
- Communicate and review existing national preparedness and response plans and provide advice on gaps and co-ordination needs between national plans.

- Share expertise and good practice with other groups working on preparedness plans for comparable health.
- Establish and regularly update a list of Community experts in appropriate areas of interest.
- Set up groups to advise on contingency planning for particular diseases.
- Advise on:
  - The activation of an OAT by the Commission in consultation with the Member States under defined terms of reference.;
  - The development, use and monitoring of use of medicinal products.
  - Detection and diagnostic capacity.
  - Community surveillance schemes on human and animal influenza; the EMEA and the WHO will be fully involved in the work of the group.

### **Outbreak Assistance Team (OAT)**

A mechanism to establish and activate an OAT consisting of experts drawn from a list established in conjunction with the Member States will be created by the Commission in collaboration with the Member States. The team should work with an agreed mandate, organisation, structure, and detachment procedures. The full range of tasks of the team may vary according to the terms of reference to be defined by the PRPG, but would include the following:

- Participation in outbreak investigation inside and outside the Community in co-operation with the WHO.
- Provision of assistance in risk assessment and co-ordination of activities on site.
- Provision of expertise and consultancy to national/local health authorities and the Commission services.
- Reporting on request to the PRPG.

## **4.2. Surveillance**

### *4.2.1. Objectives*

*Phase 0, level 1:*

Recognise new virus type.

*Phase 0, level 2:*

Ensure confirmation of the strain and identification of its source.

*Phase 0, level 3:*

Begin intensive surveillance;

Ensure rapid transmission of information on transmission characteristics with the WHO and country(ies) affected.

*Phase 1, Phase 2, levels 1 and 2:*

Ensure sharing of information on epidemiological surveillance data with the WHO and the countries affected.

*Phase 2, levels 3 and 4 and subsequent phases:*

Continue clinical surveillance to provide essential information on the extent and burden of illness and the causes of complications.

Continue sufficient virological surveillance to check on the spread and evolution of the virus, including antiviral susceptibility.

#### *4.2.2. Role of the Commission and the Member States*

The most important task of surveillance by the Member States is to provide early detection and characterisation of pandemic strains from clinical or other specimens and a reliable risk assessment as to its potential to cause widespread outbreaks in humans. Key elements are good coverage of virological diagnosis for suspicious cases, with rapid and effective characterisation of virus strains isolated from patients, and assessment of the epidemiological impact, in particular the burden of disease. Effective surveillance of influenza is a major part of ensuring a timely alert on an upcoming pandemic.

The Commission plays a co-ordinating role in the surveillance effort. The Member States are obliged to report influenza outbreaks to the Community network of communicable diseases set up by Decision 2119/98/EC. To this end, Dedicated Surveillance Networks (DSNs) have been developed. They function in accordance with Commission Decision 2003/542/EC<sup>8</sup> amending Decision 2000/96/EC<sup>9</sup> as regards the operation of dedicated surveillance networks. The influenza case definitions to be used for reporting are laid down by Commission Decision 2003/534/EC<sup>10</sup> amending Decision No 2119/98/EC of the European Parliament and of the Council and Decision 2000/96/EC as regards communicable diseases listed in those decisions and amending Decision 2002/253/EC<sup>11</sup> as regards the case definitions for communicable diseases.

In its efforts to develop a wide basis for action in the Community, the Commission has financially supported the European Influenza Surveillance Scheme (EISS) since 1999 under the terms of Decision No 647/96/EC<sup>12</sup> of the European Parliament and of the Council adopting a programme of Community action on the prevention of AIDS and certain other communicable diseases within the framework for action in the field

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<sup>8</sup> OJ L 185, 24.7.2003, p.55

<sup>9</sup> OJ L 028, 3.2.2000, p.50

<sup>10</sup> OJ L 184, 23.7.2003, p. 35

<sup>11</sup> OJ L 86, 3.4.2002, p.44

<sup>12</sup> OJ L 95, 16.4.1996, p.16

of public health (1996 to 2000). Decision No 1786/2002/EC<sup>13</sup> of the European Parliament and of the Council adopting a programme of Community action in the field of public health (2003-2008) provides the current basis for funding of surveillance schemes. The co-operation represented by such schemes is crucial for Community preparedness planning to ensure rapid information on influenza activity in Europe, in close co-operation with Member States and international organisations such as the WHO. The scheme communicates information on epidemics, in particular on situations with the potential for an imminent pandemic, to the Communicable Disease Surveillance and Response Network without delay. Data should be analysed and presented in a way that can easily be interpreted by the general public and policy makers. Secured pathways for reporting are essential for maintaining surveillance in a crisis situation.

Surveillance of influenza infections in animals, in particular in bird populations, is important, as birds may harbour a great variety of influenza virus strains. Based on the experience gained from the EU-wide survey on domestic poultry and wild birds mentioned above, a targeted surveillance programme will be further improved.

Timely communication of surveillance findings in humans and animals is essential in order to have the maximum time span to prepare for vaccine production and public health actions. High coverage of virological surveillance is technically and economically feasible within the European Union and could be achieved by supporting a network of reference laboratories and surveillance systems in the Member States. Clinical surveillance of human cases should include age-specific morbidity and mortality, and possibly also rates of hospitalisation. Clinical manifestations may change, especially during the later pandemic waves when new patterns may emerge.

The impact of vaccination programmes and other health measures should be assessed as the composition of vaccines varies from year to year. More emphasis should be placed on systematic surveillance of the impact of vaccination programmes on morbidity and mortality.

Under the terms of Proposal for a Regulation of the European Parliament and of the Council establishing a European Centre (for Disease Prevention and Control), presented by the Commission (COM(2003) 441final, 2003/0174 COD) the ECDC would be expected to assume all tasks related to the epidemiological surveillance under the plan, to take part in the organisation and conduct of influenza outbreak assistance, and to provide advice on options and guidelines for appropriate responses in the various phases and levels contained in the plan.

### **Serological studies\***

In addition to clinical and virological surveillance, serological studies would also have to be carried out. During a pandemic, serological studies should be done at the beginning of the first wave and at the end of phase 2 to predict morbidity and mortality in the age groups that will be hit the most severely by the pandemic strain.

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<sup>13</sup> OJ L 271, 9.10.2002, p. 1

\* A branch of laboratory medicine concerned with the analysis of the contents of the blood serum, in which antibodies to infectious diseases are detectable

These data should serve as a basis for realistic estimates of the need for vaccines and antivirals.

Plans should, therefore, be in place to evaluate at Community level the serological status of population groups to specified influenza viruses.

### **Laboratory preparedness**

The capability of laboratories to ensure early detection of the circulation of a pandemic strain is the key to virological surveillance.

Laboratory capabilities within Member States are essential for the early detection of the pandemic strain and for establishing the epidemiological situation. In each Member State there should be at least one laboratory that collaborates with health care facilities to obtain samples from suspected cases and collects viruses isolated in other diagnostic laboratories. It should also be able to determine the characteristics of the virus. The delay between the time the sample is taken and reporting must be short. The national reference laboratories should be designated by Member State competent authorities, and be recognised, where appropriate, by the WHO Global Influenza Programme as National Influenza Centres.

Together, under the co-ordination of the Commission and in conjunction with the Communicable Disease Surveillance and Response Network, these laboratories should form the Community network of reference laboratories for human influenza. Within this network, individual laboratories would contribute to the network in their respective fields of expertise in surveillance and research. Information, capabilities and materials should be shared in a way that ensures a uniformly high quality of virological surveillance throughout the EU.

In animal health, a Community Reference Laboratory for Avian Influenza has been established since 1992. It works closely together with the National Avian influenza Laboratories. In the future, co-operation must also be established between the animal and human influenza laboratories in the whole of the EU.

### **Vaccine coverage, effectiveness and safety**

Monitoring of vaccination coverage, effectiveness and safety for a new pandemic vaccine would have to be bolstered through surveys of target groups. Vaccine side effects should be monitored by the EISS.

## **4.3. Prevention, Mitigation and Response**

### *4.3.1. Objectives*

#### *Phase 0, level 0:*

Build up experience of handling influenza outbreaks and epidemics through routine programmes;

Establish co-operation links with and ensure training of health professionals.

#### *Phase 0, level 1:*

Initiate action to develop candidate vaccine strains in collaboration with the WHO, the EMEA and vaccine manufacturers.

*Phase 0, levels 2 and 3, Phase 1:*

Help implement mitigation and response strategies in affected countries.

*Subsequent phases until the end of the pandemic:*

Initiate action to issue clear guidance on use of vaccines and antivirals with a view to ensuring equity of access.

Implement vaccination plans, mitigation strategies involving care and use of antivirals and antibiotics where appropriate.

#### 4.3.2. *Role of the Commission and the Member States*

The risk groups for vaccination may be different from normal, i.e. young people may be at risk if a virus similar to the pandemic virus has circulated previously and older people retain some immunity. Furthermore, when vaccine is in short supply, priority may be given to maintaining essential services and reducing social disruption. Each Member State should prepare plans for vaccinating priority groups. The Commission could facilitate co-ordination of plans to ensure inter-operability and to avoid confusion and public concern over the level of health protection afforded in various parts of the EU.

Antivirals may provide some protection before vaccines become available. Member States should consider how to use limited stocks due to limited current availability, and to prioritize those who should receive the drugs during the first wave. The Commission could facilitate the exchange of information and sharing of good practice in this area.

#### **Needs and capacities for vaccines, antivirals and antibiotics in the event of a pandemic**

During inter-pandemic periods, manufacturers of vaccines, antivirals and antibiotics produce doses to meet forecasted market needs. Manufacturing capacity within the Community and in companies supplying the Community is not generally known, but it is not likely to be sufficient to meet the demands during a pandemic. Recent advances in production techniques using cell cultures and/or reverse genetics may enhance production in such situations.

Information concerning the annual use of vaccines in risk groups and the general public should be collected to provide a basis for estimates of eventual needs during a pandemic. Estimates of probable needs during a pandemic would help the annual vaccine supply process. As part of the plan the following could be pursued:

- Provision of estimates of the need for vaccines, antivirals and antibiotics from Member States according to the likely scenarios for their use.
- Determination of priority groups for vaccination, when vaccine is in short supply.

- Establishment of options for public health measures to minimise morbidity and social disruption when there is rapid accumulation of cases of influenza.
- Collection of information from manufacturers about production capacities and plans for vaccines, antivirals and antibiotics.

### **Community plan for co-ordinated production, distribution and use of vaccines and antivirals**

Currently inactivated virus vaccines are produced in fertile chicken eggs, which must be ordered many months in advance. Vaccines are recommended for groups of the population considered to be at risk. Within the Community there are only five Member States with resident vaccine manufacturers and some vaccine used in the Community is produced outside. At present, vaccine is available to all Member States under commercial agreements. Influenza antiviral agents (M2 inhibitors and neuraminidase inhibitors) are widely licensed in the Community, but their use is not widespread.

In the event of a pandemic:

There are certain constraints to vaccine production and availability. Candidate vaccine strains may be derived from animals. It is imperative that the application of veterinary import controls does not jeopardize or unnecessarily delay rapid distribution and use of viral strains in the Member States. Moreover, vaccines may be needed outside the normal production season when eggs are in short supply. This could seriously delay vaccine availability.

It may take at least 2-3 months but probably significantly longer to develop a safe vaccine strain, and possibly even longer if the pandemic virus is highly pathogenic. Time could, however, be saved by prioritization of virus sub-types from a library of reagents, to be produced in advance by the Community Network of Reference Laboratories for Human Influenza operated by the EISS in conjunction with the WHO to represent all known influenza subtypes. Such a vaccine could be used to combat the first wave of a pandemic, before vaccine is available from the pandemic virus.

Current vaccine production capacity is not deemed to be sufficient to meet the demands of the Community in the event of a pandemic. Manufacturers' reserve capacity is not likely to be enough to support a sudden increase in demand. Availability of vaccines or antivirals to populations most at risk may, in critical situations, be further limited by measures imposed by Member State authorities to provide maximum protection to their own population. Measures should, therefore, be considered with a view to ensuring equity of access. Measures should not, however, include the promotion of any behaviour in breach of EU competition rules.

### **Marketing authorisation of pandemic influenza vaccines**

The current Community procedures for the marketing authorisation of medicinal products include a Centralised procedure, involving the EMEA, and a Mutual Recognition procedure, managed and co-ordinated by the Member States CAs. The Centralised procedure is, however, mandatory for medicinal products developed by means of DNA-recombinant techniques, such as reverse genetics.

Changes to the composition of the vaccines, e.g. change of the vaccine strain are made through a variation to the terms of an existing marketing authorisation, which can take up to 90 days depending on the type of variation.

In a pandemic situation, speed in vaccine development, authorisation and distribution will be crucial. Specific legal provisions to tackle this are outlined in Article 8 of Commission Regulations 1084/2003<sup>14</sup> and 1085/2003<sup>15</sup>. Detailed guidance documents have been drafted by the EMEA and the Commission, to explicitly define how a marketing authorisation application for a pandemic influenza vaccine should be submitted<sup>16</sup>.

The proposed approach is a two-steps one, based on the concepts of a core pandemic dossier and a pandemic variation:

A core pandemic dossier is submitted and approved during the inter-pandemic period, the period between two pandemics. This dossier should enable all parameters which do not specifically depend on the pandemic, such as production processes and testing strategies, to be validated prior to the pandemic situation. A “mock-up” vaccine, ideally having the same characteristics as the intended pandemic vaccine, is to be tested in this context. This “mock-up” vaccine would not be marketed until a pandemic situation occurs in the Community and a variation application containing all relevant information on the specific pandemic strain is filed.

When the pandemic situation occurs, a pandemic variation would be submitted. This variation would contain only data that are new and relevant for the pandemic strain. The assessment and authorisation of this variation would be done in a ‘fast-track’ procedure.

In order to increase the preparedness of both the industry and competent authorities for a possible influenza pandemic, a joint EMEA-Industry Task Force (JEIF) will be set up. This JEIF would involve experts from the competent authorities, WHO, representatives from the European Directorate for the Quality of Medicines (EDQM) and the Official Medicines Control Laboratories (OMCLs), Commission representatives, manufacturers of influenza vaccines, and EMEA staff. The group would meet on a regular basis, to provide information and advice to regulatory authorities, review the status of preparedness of vaccine manufacturers, and discuss quality, safety and efficacy aspects of pandemic influenza vaccines.

In the event of a pandemic situation, other task forces specifically dedicated to the scientific evaluation of new pandemic influenza candidate vaccines may have to be set up as well.

#### **4.4. Communication**

A communications plan has to be prepared for each phase and level. The more serious the threat, the more important it will be to ensure very good and perfectly co-ordinated communication to the general public and to the media.

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<sup>14</sup> OJ L 159, 27.6.2003, p. 1

<sup>15</sup> OJ L 159, 27.6.2003, p. 24

<sup>16</sup> EMEA/CPMP/4986/03 & EMEA/CPMP/4717/03, Réf.:<http://www.emea.eu.int/indem/indexh1.htm>

Even at threat level 0 or 1 of phase 0, the perceived threat of a pandemic can give rise to considerable media interest. Making reliable information about the threat available should be a key priority of Member States and the Commission. Giving out authoritative information at an early stage will prevent the creation of an “information void” that the media may fill with speculation and rumour. To ensure they are in a position to do this, the Member State authorities should develop a range of ready to use media briefing materials about influenza. These would, for example, give a certain amount of basic information about the disease and the systems in place to respond to major outbreaks.

During an influenza epidemic, information about both EU level and national actions to address the threat will need to be communicated to the media, and the public, in a timely and consistent manner. Communication strategy needs to be considered early on in the process of addressing a potential pandemic. Member States and the Commission should endeavour to co-ordinate common messages and statements to the media about the threat and the planned measures to avoid confusion and contradictory statements.

One way of ensuring the sharing of information among Member States and openness to the public and the media will be for the Commission, during a pandemic, to publish daily reports on the Internet on influenza cases around Europe reported to the Communicable Disease Surveillance and Response Network. This way of working proved effective during the SARS outbreak.

Arrangements for vaccination and distribution of antiviral agents will vary from country to country depending on their national plans. Communicating to health professionals and to the public about these arrangements will necessarily be a task for Member State authorities. Nonetheless, even in these circumstances there will be a need for some level of EU-wide co-ordination. It will help reinforce public confidence in the response strategy if Member States and the Commission can demonstrate that the national strategies across the EU are consistent and based on a common assessment of the relevant science.

At threat levels 3 and 4 of phase 2 and in subsequent phases, there is a need to define explicit communication tasks to the PRPG and to the OIT. It would also be necessary to define adequate tools and clarify responsibilities between the communication performed by this structure and by the Commission and the Member States.

#### **4.5. Civil Protection**

A Community Mechanism to facilitate reinforced cooperation in civil protection assistance interventions has been established under Council Decision 2001/792/EC<sup>17</sup>.

Within this framework, assistance may be provided to requesting Member States, Acceding and EEA/EFTA Countries in the event of a pandemic with serious consequences requiring the activation of civil protection emergency plans.

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<sup>17</sup> OJ L 297, 15.11.2001, p.7

#### **4.6. Research**

The research components of various Community actions have already been identified in the Community's 6th Framework Programme. Research performed during the inter-pandemic period is vital for preparing for effective pandemic response.

Research leading to the development of new vaccine technology should remain a priority and be linked to routine and fast-track licensing procedures for influenza vaccines.

Current and emerging anti-viral drug resistance developments in influenza need to be addressed through coordinated research at the European level<sup>18</sup>.

Furthermore, in the process of early recognition of the identity and origins of pandemic strain, the role of international scientific cooperation is key. The Commission will therefore continue to develop its collaborative research networks to integrate partners in third countries, as was the case in the past with similar threats, such as Ebola and Lassa fever and more recently SARS.

#### **5. PREPAREDNESS AND RESPONSE TO INFLUENZA PANDEMICS : MAIN ACTIONS**

The key actions to be planned and implemented in regard to influenza pandemics can be grouped under the phases and levels presented in chapter 3. Different sets of action have to be undertaken by the Commission and the Member States, but there are also actions that have to be carried out jointly. Actions are assembled for various phases and levels to be advised by the PRPG following the assessment of the epidemiological situation on the basis of the criteria set out in the table of correspondence.

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<sup>18</sup> A total of 9 million € has been allocated from the 6th Framework programme to set up a vigilance research network for the management of anti-viral drug resistance in influenza and viral hepatitis B and C. The proposal is currently under negotiation with contract launch foreseen during spring 2004.

*Phase 0, level 0:*

### **Commission**

Maintain records of status of Member States pandemic preparedness and response plans.

Review the possible legislative restrictions on the transport of virus strains or isolates necessary for vaccine production across Member States and consider and prepare ways to ease them for the purpose of public health protection.

Establish an inventory of Community experience of reverse genetics techniques.

Explore possibilities for an accelerated central authorisation procedure for vaccines and analyse the implications of new vaccine production technologies on vaccine licensing and quality assessment.

Address issues of research and development, authorisation and availability of new vaccines through the Commission Pharmaceutical Committee set up by Council Decision 75/320/EEC.<sup>19</sup>

Examine the feasibility of setting up a mechanism for co-ordinated production, distribution, stockpiling and use of vaccines, antivirals and antibiotics ensuring equity of distribution at Community level in the event of a pandemic.

Prepare some ready to use media briefing materials on influenza. These should, in particular, give basic information about the EU's role in responding to a major influenza outbreak.

### **Member States**

Complete, review, update and implement national influenza pandemic preparedness and response plans.

Establish a National Pandemic Planning Committee (NPPC) to advise on influenza pandemic measures.

Competent authorities to designate National Reference Laboratories for Human Influenza to be recognised, where applicable, by the WHO's Global Influenza Programme as National Influenza Centres, and inform the Commission on such designations.

Achieve high vaccine coverage, in particular in vulnerable groups, such as health care workers and the elderly, in line with paragraph 1 of the Resolution of the Executive Board of the WHO of 23 January 2003 on Prevention and control of influenza pandemics and annual epidemics<sup>20</sup>.

Prepare some ready to use media briefing materials on influenza. These should, in particular, give some information on the national preparedness plans.

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<sup>19</sup> OJ L 147, 9.6.1975, p.23

<sup>20</sup> [http://www.who.int/gb/EB\\_WHA/PDF/EB111/ceb111r6.pdf](http://www.who.int/gb/EB_WHA/PDF/EB111/ceb111r6.pdf), accessed 17/11/2003

## **Commission and Member States**

Establish a Community Network of Reference Laboratories for Human Influenza within influenza surveillance schemes in the Community and develop a protocol for sending appropriate specimens.

Maintain an inventory of laboratory capacities and facilities available at national level in the Member States.

Strengthen co-operation of Community surveillance systems on human influenza with influenza surveillance networks operating outside the Community.

Create and maintain links between human and veterinary surveillance systems.

Improve ongoing clinical, epidemiological and virological surveillance, building on existing structures.

Co-operate with the WHO and the EMEA on the development of new vaccines.

Maintain continuous dialogue with the pharmaceutical industry;

Improve surveillance of vaccination coverage and effectiveness in the current priority groups during the inter-pandemic phase.

Evaluate pandemic plans and co-ordination during pandemics.

Support the modelling of pandemics through EU-wide exercises and define, characterise and monitor different high-risk groups according to different scenarios.

*Phase 0, levels 1, 2 and 3; Phase 1:*

### **Commission**

Convene as appropriate the PRPG to consider and agree on guidelines.

Maintain regular contact with the WHO and provide assistance for outbreak investigation, including that involving the OAT, if requested by the WHO.

Jointly with EMEA :

Convene a meeting of the JEIF after the announcement of Phase 0, level 3. Issues to be discussed at this meeting should include: identification of the manufacturers of pandemic vaccines and production capacities, status of the marketing authorisations and timelines for submissions of pandemic variations, status report on the official release testing of the pandemic influenza vaccine batches.

Manage and coordinate the fast-track assessment of the submitted variation application, as soon as the timeline for submission of a pandemic variation is known.

### **Member States**

Review and update the national pandemic preparedness and response plans, where appropriate, following advice by the National Pandemic Planning Committee.

Provide, if requested by a Member State, assistance for any further investigation, in accordance with the provisions of Annex II to Commission Decision 2000/57/EC.

Ensure laboratories involved in typing viruses review their techniques and materials, and prepare status report of reagents and diagnostic capability for novel subtypes.

Institute virological sampling in areas where the population may have travel-related contact with the site of initial identification of the novel virus.

Report possible clusters or outbreaks of influenza-like illness and clinical and epidemiological characteristics of the new influenza subtype using the Community's Early Warning and Response System set up under Decision 2119/98 and communicate information on the nature and scope of the potential threat and the measures to be taken.

### **Commission and Member States**

Maintain close and effective collaboration with the producers of anti-viral and anti-bacterial drugs as well as the vaccine manufacturing industry;

Consider co-ordination of communications vis-à-vis media and public.

*Phase 2, level 1 and 2:*

### **Commission**

Start publishing, via the Public Health website, the Early Warning and Response system reports on pandemic Influenza cases in the affected regions.

### **Member States**

Initiate national response measures according to pre-determined national pandemic plans. Obtain advice from the National Pandemic Planning Committee if new information has come to hand which necessitates amendments to the preparedness and response plan.

Have specific pandemic surveillance plans in place to be able to provide information on the time the virus was introduced in their territory, on the severity of the pandemic virus and on the capacity of health systems to cope with challenges, in accordance with Decision 2119/98/EC and Commission Decision 2000/96/EC<sup>21</sup> on the communicable diseases to be progressively covered by the Community network under Decision N° 2119/98/EC of the European Parliament and of the Council.

Evaluate provisional data on regional morbidity and mortality and carry out risk assessment.

Circulate samples of suspected pandemic strains as well as appropriate rapid diagnosis reagents to the reference laboratories.

Intensify production of reagents for diagnosis not following reference standards.

Continue the validation of novel diagnostic tests.

Identify appropriate near-patient tests for influenza and monitor use and results.

Establish surveillance of clinical conditions which have been linked to novel virus.

Assess validity of routinely collected clinical influenza indices.

Intensify virological characterisation of influenza isolates.

Implement rapid dissemination of information gained from enhanced clinical and virological surveillance activities.

Assess new medicines and if necessary undertake batch release of vaccines manufactured nationally.

Take necessary steps to improve supply of vaccine against the new virus.

Ensure that :

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<sup>21</sup> OJ L 28, 3.2.2000, p.50

- adequate measures are initiated, with a view to finalising decisions on priorities for the use of available vaccines and antiviral drugs.
- priority groups are offered vaccination.

Take steps to ensure that the health services have access to sufficient quantities of medicines.

Decide on measures to increase the treatment capacity in the municipal health services and hospitals.

Ensure that adequate and co-ordinated information is given to the health services and the general public about the development of the pandemic.

Affected Member State(s) to inform the Member States and the Commission without delay, via the Early Warning and Response System of the nature and scope of the potential threat, the measures intended to be taken and the results of the measures taken.

### **Commission and Member States**

Activate, if appropriate, under the terms of Decision 2001/792/EC<sup>22</sup> the Community mechanism to facilitate reinforced co-operation in civil protection assistance interventions in Member States, Acceding and EEA/EFTA countries or countries outside the EU that might be affected.

Commission to co-ordinate together with the Member States via the Early Warning and Response System, further measures to be taken at Community level, especially those concerning advice to travellers, occupationally exposed staff and other groups at risk, following the advice by the PRPG.

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<sup>22</sup> OJ L 297, 15.11.2002, p.7

*Phase 2, levels 3 and 4:*

### **Commission**

Convene the PRPG, activate the OAT and continue using the Early Warning and Response System for information on and co-ordination of measures.

### **Member States**

Continue the actions started in phase 2, levels 2 and 3.

Develop specific reagents and ensure that laboratories have adequate supplies and Standard Operating Procedures for identification of new viruses.

Monitor data on influenza activity across the country and in population subgroups.

Investigate and document outbreaks, including efficacy of any appropriate control measures.

Implement data collection for studies related to outcomes of influenza in identified risk groups.

Review information on co-pathogens in influenza cases.

Refine antibiotic and symptomatic treatment guidelines based on data collected as mentioned above.

Produce characterisation of all influenza novel viruses for preparation of candidate vaccine strains.

Compare virological data from national and international sources.

Monitor antiviral susceptibility of virus isolates and compare data with other international sources.

*Phase 3:*

**Commission**

Continue actions started in phase 2, levels 3 and 4.

**Member States**

Continue the actions started in phase 2, levels 3 and 4.

Collate and assess information on impact of pandemic on communities and hospitals.

Reduce active surveillance in favour of detection and analysis of strains from hospital cases.

Concentrate on identification of antigenic drift in novel strains, antiviral resistance or emergence of other variants.

Continue surveillance of secondary bacteriological infections to help develop antibiotic treatment policy.

Liaise with distributors of vaccine, if vaccine available, for monitoring of vaccine uptake.

*Phase 4:*

**Commission**

Continue the actions of phase 3.

Evaluate experience gained and review the Community Plan, where necessary.

**Member States**

Continue the actions of phase 3.

Review national preparedness and response plans, where necessary.

Inform the other Member States and the Commission of the effects of the pandemic.

Continue monitoring global spread and impact of virus.

Estimate remaining need for vaccines and availability of antiviral drugs.

Monitor any antigenic drift in the virus and its significance if detected.

**Commission and Member States**

Maintain the relevant measures as stipulated for phase 2, threat levels 3 and 4 with the revisions introduced during phase 3.

*Phase 5:*

**Member States**

Inform the other Member States and the Commission of the effects of the pandemic.

**Commission and Member States**

Assess the overall impact of the pandemic.

Evaluate experience gained and review the Community and the national Plans, where necessary.

## 6. CONCLUSIONS

This paper outlines the key elements and sets of actions that may constitute the components of the Community Influenza Pandemic Preparedness and Response Plan for discussion and conclusions on the appropriate follow-up. It is important that these elements be given consideration as a matter of urgency and that they fuel the necessary political debate and help steer concrete actions. The latter can take the form of recommendations or binding measures, such as a Commission decision, within the context of the existing Community legislative framework in the field of public health.

Furthermore, as set out in the recommendations of the influenza pandemic preparedness planning conference held in 2001, closer co-operation should be sought between human and animal health authorities and experts in the area of influenza virus infections. In this context, a mutual exchange of experiences in contingency planning could be of major importance, as contingency plans in animal health are already well established and have proven to be effective in the past.

Preparing and responding to influenza pandemics would present a formidable challenge and would require increased efforts by the Member States and the Commission. This should be done as part of a more general approach to public health emergencies, in order to use scarce resources effectively, benefit from the widest possible expertise and keep procedures and functions manageable and as simple as possible. To this end, the Commission has proposed creating a European Centre for Disease Prevention and Control (ECDC), which can provide a structured and systematic approach to the surveillance and control of communicable diseases and other serious health threats that might affect the people of the European Union. The creation of a European Centre would mobilise and significantly reinforce the synergies between the existing national centres for disease control and would no doubt help the Commission and the Member States to deal effectively with influenza. The ECDC would be expected to assume all tasks related to the epidemiological surveillance under the plan, to take part in the organisation and conduct of influenza outbreak assistance, and to provide advice on options and guidelines for appropriate responses in the various phases and levels contained in the plan illustrated in this paper.