22 April 2005

Towards sufficiency of Pandemic Influenza Vaccines in the EU

Summary

The strategy advocated by the Commission on Community influenza preparedness and response planning was outlined in a working paper published in March 2004[1]. Key aspects of this strategy are the preparation of preparedness and response plans by the EU Member States and their inter-operability at EU level, outbreak management through advice, early notification of cases, outbreak assistance and coordination of responses of Member States, surveillance and networking of national reference laboratories to identify the pandemic strain quickly and availability of vaccines and anti-viral drugs.

In its conclusions adopted at the meeting on June 2004[2] the Council acknowledged the plan, and identified as priorities the drawing up and inter-operability of national plans, the development of a high-performance network of reference laboratories and the engagement with the pharmaceutical industry in discussions to foster the availability of a better vaccine in sufficient quantities.

Furthermore, the Council extended the mandate of the Health Security Committee (HSC) to cover influenza pandemic preparedness and response planning for a period of one year and asked that the position be reviewed when the European Centre for Disease Prevention and Control will be in place (May 2005).

The Health Security Committee, following this mandate, has worked with the Commission to implement key components of the strategy. The work has focussed on improving availability of vaccines and antivirals and the drawing up, coordination and testing of national plans through scenario exercises to test communications and interoperability of national preparedness plans.
At its meeting on 6 December 2004, the Council was informed on the state of play on influenza pandemic preparedness planning at Community level, in particular on the ongoing constructive dialogue between the representatives of the Member States and the pharmaceutical industry on influenza vaccines.

On national plans, the work undertaken under the Council mandate benefited from cooperation with the WHO-Regional Office for Europe and has proved instrumental in helping Member States to review, update and improve their preparedness and response plans and to identify key issues for urgent attention in the future that the Commission is taking forward with the WHO.

On antivirals, the efforts undertaken have led to benefits for Member States in terms of insights and crucial information about the acquisition of antivirals, their use and limitations and stimulated an interest in the pharmaceutical industry for involvement of more companies in this crucial public health area which would undoubtedly benefit Member States and public health in general.

[1] COM (2004) 201 final, 26.3.2004

[2] SAN 104, 9882/04, 2.6.2005

This paper addresses the remaining element of the Council Mandate, namely, progress with the work on pandemic influenza vaccines. It sets out recommendations, agreed with the HSC, for a strategy for creating conditions of sufficiency in such vaccines in the EU and outlines a public-private partnership (PPP) between public bodies and the vaccine industry to deliver influenza vaccine to the European Union population in the shortest possible time in the event of an influenza pandemic which can also be used for the production of vaccines in a solely public framework for the Member States that follow that option. In the latter case, "industry" would refer to the public sector-owned vaccine manufacturer and PPP would represent a public-public partnership.
Industry's stated contribution to the PPP is the development of the prototype influenza vaccines in accordance with the EMEA Guidelines and the candidate vaccine in case of pandemics. Industry will ensure the production of the pandemic vaccines, using the facilities available at the time of the pandemic.

The public sector would support industry starting with the development of a library of seed stocks for manufacturing of influenza vaccine. It could furthermore provide support for clinical trials for the mock-up vaccine and development of post marketing surveillance systems. It would assist the industry in the clinical trials and data gathering of alternative vaccine formulations, including varying doses of antigen and the use of adjuvants. The public sector would further undertake serological and animal challenge studies to provide scientific evidence for the likely protective efficacy of candidate vaccines against a particular circulating pandemic strain. The time saved in having a vaccine available for public use by these activities is potentially 2 to 3 months and possibly more.

Industry would be expected to manufacture trial lots of vaccine and to submit core pandemic dossiers for different mock up vaccine strains in accordance with the latest guidelines on pandemic vaccines issued by the EMEA.

Part of the public contribution would be to increase the use of interpandemic influenza vaccine by ensuring that uptake is raised to the levels recommended by the World Health Assembly resolution 56.19.

Funding of the work to the establishment of the partnership could be provided from the public sector through the EU Public Health Programme and Member State contributions to co-funded projects under the Public Health Programme, and for manufacturers by the industry. Regulatory support is being provided to industry through existing mechanisms of cooperation in which EMEA plays a central role and through the waiving of fees for mock-up dossiers and scientific advice from the EMEA.

The work undertaken under the Council's mandate in this area has produced already results in providing useful insights for the Member States to negotiate with industry and has prompted the industry to start producing mock-up files and reviewing costs and prices, as well as stimulating more companies to be involved in the production of vaccines.;

1. Introduction

This paper puts forward the outlines of a "public private partnership (PPP) between the EU Member States, the Commission and the European Vaccine Manufacturers for the development and availability of pandemic influenza vaccines.

The PPP is based on a two-tiered approach: A sustainable increased interpandemic influenza vaccination uptake ("pull"), in the framework of existing Member States' vaccination policies, is linked with a structured initiative for a product development plan

("push") to accelerate the timely production of the appropriate pandemic vaccine by industry through specific underpinning contributions from the public sector and appropriate financial incentives.

Industry's contribution to the PPP, as set out below, is the development of the pandemic influenza vaccine. This includes vaccine formulations, clinical lot production, pre clinical testing, clinical testing, mock-up registration file, production scale-up and shipment and delivery.

The proposed public sector contributions entail the provision of:

1. a library of vaccine seed stocks;
2. vaccination effectiveness and efficacy studies including the assessment of protective efficacy of different vaccination regimens in animals and man;
3. monitoring of vaccination uptake in the Community;
4. the establishment of correlates of protection to effectively determine the cross-protective efficacy of pandemic vaccines;
5. a firm commitment by all EU Member States to increase interpandemic influenza vaccine uptake in line with WHA recommendations.

2. Background

The Commission services and the Member States representatives in the Medicines Group of the Health Security Committee reviewed industry proposals for an action plan for pandemic influenza preparedness submitted in February 2004 by the European Vaccine Manufacturers (EVM) to the Commission and the Member States[3]. EVM states that the average cost to develop a prototype vaccine is estimated at about 11 Mio Euros for one mock-up dossier, and there could be potentially 10 such dossiers to be submitted by the various companies concerned. EMEA guidelines on submission of marketing authorisation applications and on dossier structure[4] aim to guide the production of a prototype vaccine (and the associated mock-up file) with a single strain (the most likely candidate pandemic strain being the H5N1 strain currently afflicting poultry in Asia) to allow an abbreviated filing registration procedure once the pandemic is declared and the final strain is identified by WHO.

This paper is the result of a consultation process between industry and the members of the Health Security Committee and its Medicines Working Group. The Commission will submit a paper to the Council for consideration by the Health Ministers at their meeting on 2-3 June 2005 that takes into account this document which was endorsed by the HSC at its meeting on 18-19 April 2005. If there is sufficient interest in participation by the Member States, the Commission would implement the PPP with appropriate instruments.

[3] Communication to the Commission by the EVM, "Influenza Pandemic Preparedness. EVM Proposal for an Action Plan between EVM and Member States with the support of the European Commission", February 2004

[4] EMEA/CPMP/4986/03 & EMEA/CPMP/4717/03, Réf.:http://www.emea.eu.int/indem/indexh1.htm

3. Objectives

The objective of the PPP is to engage the European Community, the Member States and the vaccine manufacturing industry on improving the supply and availability of pandemic vaccines to provide the best possible cover for the European Union population against the risk of pandemic influenza. What the PPP is expected to deliver is the production of the most effective pandemic vaccine in the shortest possible time in sufficient quantity for the EU population.

This will be achieved through a set of ***specific*** objectives:

(1) More rapid development

☐ **Facilitate development**

☐ **Facilitate rapid production using conventional techniques**

First of all there would be an advantage in making available Good Manufacturing Practice seeds compared to current attenuated reference strains and some of the testing will be performed by the public partner(s) instead of by the individual manufacturers. The use of such library strains will also speed up the production of clinical trial lots of mock-up vaccines and will therefore facilitate the preparation of the relevant dossiers. In addition, provided that the library seed strain shows good cross-protection against the actual pandemic virus, manufacturers could also use the library seed to produce pandemic vaccines. The time gain of this approach could be up to several months, especially if the pandemic would strike quickly with no (fully matching) pandemic seed stock being available within the first months after the announcement of the pandemic. As cell culture systems become available, this library of seed strains will be extended to include appropriate seed stocks for the extant cell culture processes.

(2) More effective vaccines

☐ **More effective regimens (one or two doses)**

☐ **Facilitate development of improved formulation (use of adjuvant, reduced antigen content)**

(3) Better availability by increasing production capacity

☐ **Increase and monitor interpandemic coverage, by:**

- engaging EU Member States in increasing their influenza vaccination coverage in the elderly as set out in their own vaccination programmes and the current high risk groups, according to WHA resolution 56.19;
- performing vaccine cost effectiveness studies with a view to establishing public health based criteria in relation to vaccine recommendations.

☐ **Create incentives for producers to maintain spare capacity**

☐ **Improve production processes (e.g. cell-based) by**

- supporting the development of cell culture processes with can be deployed to secondary manufacturers such as veterinary vaccine manufacturing plants;
- engaging in the development of GMP seeds also for cell culture processes.

(4) Encourage Member States' governments and the Commission to address vaccine-usage key issues

☐ **Liability**

Exposure to liability differs from normal marketed vaccines. In the case of an influenza pandemic, tight deadlines will have to be met and health authorities in the Member States will urgently need the pandemic influenza vaccine for mass vaccination. Mass vaccination campaigns could be marked by the occurrence of adverse events. This issue should be properly addressed by the PPP and recommendations made to the Commission and Member States.

☐ **Safety issues other than due to effects of manufacture**

☐ **Availability of the products to all Member States by**

- Providing advice and recommendations to the Commission and Member States;
- Promoting equity of distribution among Member States and accessibility to pandemic influenza vaccines while taking into account availability to non-EU countries (EU manufacturers export a significant part of their production).

The PPP would seek to obtain a greater risk reduction: if a significant number of core dossiers on pandemic mock up (candidate) vaccines, derived from different reference virus strains, would exist today, then a greater area of risk would be covered. The industry is invited to proceed with the speedy tabling of mock up dossiers for registration in respect of marketing authorisation.

Presently there are possibly one or two core dossiers being developed, but they are understood to be based on the H5N1 strain only. Even in the case of several dossiers being submitted, based upon H5N1, this would not significantly increase the knowledge database on candidate pandemic strains, as the differences between these dossiers might be largely regulatory. This is largely due to the current emphasis placed upon H5N1 in view of the perceived high risk associated with this strain which has become endemic in animals in Asia.

4. National approaches for pandemic influenza vaccine preparedness

Several national plans of pandemic influenza vaccine preparedness are heavily dependent on the presence of a local manufacturer within the borders of the country concerned. Arrangements for supply consist of a combination of a long term commitment for annual purchase of inter pandemic vaccines with a pandemic readiness fee to allow for manufacturing capacity to rise to pandemic sufficiency levels, and a long-term commitment to purchasing a number of vaccines when the pandemic comes that is deemed appropriate to face up to the pandemic (this is normally taken to correspond to the number of inhabitants). Two examples are Hungary and Canada which has developed a national advance purchase agreement (NAPA) with a local manufacturer for this purpose.

5. Basic research

A comprehensive contribution to an enlarged EU research agenda on pandemic influenza for the EU has recently been compiled in a published paper[5]. The paper

addresses short term (antigen sparing strategies[6]) and long term (a broad spectrum cross protective pandemic influenza vaccine) research goals.

It is expected that a potential new integrated project submitted to the Commission (in response to a recent 6th Framework Programme of Research call for proposals on post-genomic approaches to a human pandemic influenza vaccine) will address certain elements of this agenda. If this project is selected for funding, care will be taken to ensure that it complements and not overlaps with the proposed PPP.

6. Key elements of the proposed partnership

- ***Management and administration***

Support of the PPP could be provided through the EU Public Health Programme, starting with its establishment and initial management set-up. Member States would support operations in accordance with their priorities.

A useful but not directly applicable example exists in the form of the European Malaria Vaccine Initiative (EMVI), which is built on a Product Development Plan that addresses the entire vaccine value chain from the pre-clinical phase to phase 1-3 to distribution and post marketing surveillance. Elements to be identified in this chain include research assets (public sector contribution (funding or in kind) and development assets (industry funds or industry sub-contracts). The Commission might support an outreach activity to Asian research institutions in the epicentre of the potential influenza pandemic.

In the case of pandemic influenza vaccines, the focus should be on assembling a small set of immediately available technical elements and on engaging the Member States and industry into a wider development agenda. The technical elements are to be funded by already ongoing or planned routine Members States activities, by taking over under the PPP the results of Framework Programme 6 research projects and other projects funded by the Commission.

- ***Underpinning of vaccine development by Institutions in Interested Member States***

The Health Protection Agency in the UK, the Netherlands Vaccine Institute in the Netherlands and the Statens Serum Institut in Denmark have come together and worked with the Commission to propose a coalition of like institutes in the Member States to support the PPP. They have skills in research and manufacturing that can be combined to provide a European capability to underpin the vaccine industry in preparing for an influenza pandemic.

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5 David Fedson et al. Preparing for Pandemic Influenza: A research agenda for the European Union during the interpandemic period. Background Paper for the Priority Medicines Project for Europe and the World. "A Public Health Approach to Innovation. October 2004, 46 pages.

[6] Antigen sparing: this can be done by the use of intradermal administration. A reduction to 40% or less can be achieved in this way (N Engl J Med 2004; 351:2295-2301, Nov 25, 2004). Also adjuvants can reduce the dose of antigen and several vaccine producers have already experience in these fields (Virus Res. 2004 Jul; 103(1-2):163-71.; Virus Res. 2004 Jul; 103(1-2):139-45; Infection. 2004 Aug; 32(4):191-8.)

The programme outlined in Annex 1 is designed to underpin these efforts by providing a library of seed stocks for vaccines against potential pandemic influenza viruses, by developing new production techniques that can be used in a wider range of facilities than traditional egg-based processes, and by assessing the protective efficacy of different vaccination regimens in animals and man.

The programme takes into account the industry's appeal for help with respect to the development of a prototype vaccine that can serve as a mock-up vaccine in a core-dossier application at EMEA which was estimated to cost about 11 Mio €.

EVM has listed the following parameters to develop a prototype pandemic vaccine:

- Adaptation of manufacturing area to procude Genetically Modified Organisms – GMOs- (validation procedures and decontamination SOPs against influenza virus, protection of workers during the manipulation of an avian virus;
- Preparation of specific master and working virus seeds for manufacturing;
- Manufacturing of monovalent batches and clinical lots at pilot scale;
- Development of a monovalent formulation specific to a pandemic vaccine (current vaccine being trivalent);
- Toxicological tests on animals;
- Clinical studies including evaluation of antigen concentration, use of adjuvants and dose regimes;
- Regulatory activities (Common Technical Development –CTD-; documentation for clinical studies).

A successful partnership based upon this approach would mean that the existing EU assets are used in the shortest possible time frame and that the public sector would work together with industry to streamline the manufacturing process by standardised protocol and test systems in order to meet "industry" grade material requirements. The use of GMP library seeds would significantly shorten the time period required to get pandemic vaccines available up to 3-4 months after onset of a pandemic provided sufficient cross-immunity by the vaccine antigen and the pandemic antigen exists. If not, a new vaccine will be needed based upon the circulating virus, which will take approximately 6-7 months.

It would also broaden the database by providing the industry with a seed stock library and provide an opportunity for industry to work in multi-country setting for clinical development.

Specific elements in this approach are:

1. The development and testing of a seed stock library to a stage suitable for distribution to manufacturers as a master seed lot. This part of the programme involves working together with the WHO collaborating laboratories in the partner nations, and in other countries to obtain new strains of influenza as they appear. Many WHO laboratories maintain their own collections, but the key part of this step is to have a single defined reference collection, verified and catalogued. The expertise of the WHO centres will be used to determine which isolates are significantly different from strains already held and merit inclusion as representative strains in this collection. The collection will include representatives of all the major types and sub-types. These collections are maintained by the WHO Influenza Collaborating Centres at Mill Hill, the National

Institute for Biological Standards and Control (NIBSC) in the UK and the National Influenza Centres in the Netherlands and France. These collections would be continuously updated, including the most recent circulating influenza viruses.

2. Studies on the immunogenicity of candidate vaccines in animal models first and subsequently in clinical trials using conventional haemagglutination inhibition assays. To investigate the degree of cross protection of seed stocks and existing vaccine candidates against relevant wild type strains, a small number of vaccine strains will be tested for protection in animal models. The ferret model of influenza is well established and is believed to correlate well with human disease, using fever and viral load in lung washes as indicators of infection. Carefully designed experiments will enable the effect of different previous exposures, e.g. to H1N1, to be determined when combined with vaccination by a single or two-shot regimen of a new vaccine (e.g. H5N1) against a challenge with a wild type virus (in this example H5N1). It will also allow the protective efficacy of stockpiled vaccine such as the H5N1 candidates being made in some countries, to be tested against new strains of the same main type when they emerge, either giving reassurance or prompting work on developing a new vaccine seed. This data would form part of the core dossier required to license candidate vaccine processes as described in the EMEA pandemic influenza guidelines, and would also be used to determine the likely dosage regimen.
3. Testing of cross-protection provided by selected candidate vaccines against various wild type viruses in animal models.
4. Additional immunological studies to refine the understanding of the correlates of protection for present and future vaccines.
5. Establishing and performing relevant serological testing of serum samples from clinical studies in collaboration with the EDQM (European Pharmacopoeia) in order to qualify these tests for regulatory purpose.
6. Collaboration with manufacturers through established public health networks and laboratories in the partner nations in monitoring the safety and efficacy of pandemic vaccines.
7. The proposed contributions should be in line with the regulatory requirements for pandemic influenza vaccines put forward in the CPMP Note for Guidance.
8. Cooperation with the WHO will be reinforced to ensure that the system put in place by the WHO to provide the appropriate strain to industry benefits directly from the PPP.
9. The proposed animal studies animal studies (dose/ranging studies in ferrets could be a good indicator for protection in humans) and clinical and serological protocol standardisation contributions would complement the common clinical protocol established by EVM.
10. Setting up immunisation status, vaccination rate, and adverse effect monitoring programmes under the auspices of the ECDC and EMEA.

- ***Underpinning the PPP by increasing interpandemic production capacity and vaccine coverage in all Member States***

Industry considers these as a firm commitment on behalf of individual Member States towards pandemic preparedness planning. It is predicted that when all Member States plans and pandemic needs are evaluated, projected demand for vaccines will exceed total production capacity. Industry expects that this will lead Member States to commit

to increasing coverage during inter-pandemic period with a view to increasing installed production capacity. Setting national advance purchase agreements (NAPAs) in Member States would help to achieve equitable distribution by matching capacity with total pandemic demand. There is a crucial need, however, for national plans and relevant uptake coverage, to be coordinated and evaluated by the Commission on behalf of the EU. This could result in shortfalls in one member state to be made good by contributions from others with spare capacity. In this respect, it would be useful to establish a scorecard of member states' preparations. If necessary, a complementary APA may be considered at EU level.

In their proposal of February 2004 the industry expressed the view that the Member States should engage into a commitment to increase vaccination coverage rates in the existing risk groups, and to extend influenza vaccine recommendations to subjects aged 50 years and also children, during the inter-pandemic periods (fig 10). This should answer a public health need by reducing influenza morbidity and outbreaks and ensure the development of production capacities that would allow production of enough pandemic vaccines to protect the population of the European Union, should the need arise. This could be achieved by:

1. Meeting the WHO recommendation to attain vaccination coverage of the high-risk population of at least 75% by 2010. So far, on average, 62% of the population aged 65 years and above is vaccinated annually, and much less in people at increased risk for complications of younger age. For instance in the US, it is estimated that 29% of people aged 50 to 64 years have at least one high-risk medical condition [5];
2. Extending national recommendations to younger age groups. Age-based strategies are more successful than patient-selected strategies. The group aged 50-64 represents the current target–because this group has an increased prevalence of persons with high-risk conditions (29%). Persons aged 50-64 years without high-risk conditions also receive benefit from vaccination in the form of decreased rates of influenza illness, decreased work absenteeism and decreased need for medical visits and medication, including antibiotics. Further, 50 years is an age when other preventive services begin and when routine assessment of vaccination and other preventive services have been recommended[6].
   Recommendation for universal vaccination of people aged 50 years and over has been adopted in the US in 2000. Canada has also extended its influenza vaccine recommendations to healthy people[7]. In the EU, Belgium has adopted this recommendation, while Germany and Austria have decreased the age cut-off for universal influenza vaccination to 60 years of age. As an example, illustrated in figure 10, 5-year increments from 65 and over down to 50 and over between 2004 and 2010 (i.e.: 09/2004 : 64-60, 09/2006 : 59-55, 09/2008 : 54-50) would allow, given basic assumptions, demand to be met for 50% to 100% of the European population.
3. Considering wider influenza vaccine recommendations in children. Direct and indirect epidemiologic evidence indicates that influenza is a significant health

[5] Morbidity Mortality Weekly Report 2003;52:RR-8

[6] ACIP 2003 flu vac recommendations - MMWR.pdf>> <<US flu vac cover 50+ MMWR Oct 17, 2003 .pdf

[7] Canadian Communication Disease Report 2003;29:DCC4

hazard for all children and has a socio-economic impact on healthy children and their family[8]. Because children aged 6-23 months are at substantially increased risk for influenza-related hospitalisation, the US Advisory Committee for Immunization practices (ACIP) as well as the American Academy of Paediatrics, encourages vaccination of all children in this age group[5] Such a policy has also been adopted in the province of Ontario in Canada, where universal flu vaccination is recommended. In the EU, Austria is the first EU Member State to recommend universal vaccination of children 6-23 months.

Member States representatives in the HSC and its Medicines' Working Group reviewed these elements put forward by the industry and other available evidence.

Changes in recommendations towards adults younger than the current age limits (60/65) or in children are not being considered at this stage. Any such change would have to be based on solid evidence-based public health grounds supported by an international (EU-wide) peer reviewed cost-effectiveness study.

Simonsen et al[77] studied coverage in existing target groups and concluded in a very recent publication: "we could not correlate increasing vaccination coverage after 1980 with declining mortality rates in any (studied) age group".

The additional annual investments at the level of the Member State necessary to implement the WHA resolution were estimated by *Kroneman et al*.[8] to be considerable for some countries. Poland, for example, would need to expend annually around 53 Mio Euro for vaccination, including distribution and administration costs.

EU-wide co-ordination of country-specific monitoring of vaccine uptake using population surveys that could be undertaken, for example, by the EISS influenza surveillance scheme that is co-funded by the Commission, would be an important underpinning element of the PPP.

EVM has indicated that full implementation of the WHA resolution of 75% coverage in elderly and risk groups in the EU would, according to their calculations, still leave a gap of about 30 million doses compared to what will be needed as installed capacity to produce enough (monovalent) vaccines in the case of a pandemic (which may, however, require more than one vaccination at the time of the pandemic). Actual capacity in the EU is for about 160 million doses of (trivalent) inter-pandemic vaccine production, 90 million of which cater for current EU needs. Impact of projected demographic increases in age on doses sold would be less than 1% annually.

In conclusion, Member States and the Commission were unanimous that the current national recommendations and policy, in particular the target groups would be the only basis on which inter-pandemic coverage can be increased. If there is any change to be made to national policies it will have to be done on solid public health and cost-effectiveness grounds. They are prepared to add into the partnership additional efforts to implement the WHA resolution to reach 75% coverage in the existing

[8] Pediatric Infectious Disease Journal 2003;22:10 Suppl

[7] Arch Intern Med. 2005; 165:265-272.

[8] Communication to the Commission, "Presentation to the Technical Expert Meeting on PPP", January 2005, Luxmbourg.

recommendation groups (elderly and high risk groups), working towards adopting and adapting good practice from the best performers in the EU in order to achieve this. The Commission and the Member States could review, together with the WHO, recommendations, especially as regards groups other than the elderly.

- ***Underpinning the PPP through equitable distribution of pandemic vaccines***

The Commission could work with the Member States to ensure equitable supply through an EU framework or instrument to guarantee free export from producing to non-producing countries in case of an influenza pandemic and in order to underpin the application of any NAPAs that may have been agreed.

As a significant part of the European production is exported to markets outside the EU (South America, Middle East, Africa and Asia, except Japan), the Commission and the Member States should work with the industry to agree recommendations on how to accommodate the needs of neighbouring and other third countries in case of a pandemic.

7. Framework

Following the discussions with the Member States and EVM, there is broad agreement that the proposed PPP should contain the following elements:

1. An initiating "underpinning" project that includes management and coordination of the PPP;
2. GMP virus seed vaccine library development and maintenance;
3. Efficacy studies:
   a. Pre-clinical testing (efficacy studies including correlates of protection);
   b. Clinical trial capability EU wide, possibly multi-centre to be done by the industry, supported by public sector (assays);
4. PMS [9]: post-approval clinical investigations; industry is to set up a PMS for vaccines, in cooperation with the Member States;
5. Vaccine uptake studies, cost-effectiveness studies.
6. Monitoring of vaccination targets per Member State, immunisation status and adverse effects as well as vaccine production capacity increase by industry;
7. Drawing up of EU-wide vaccination recommendations;
8. Arrangements for equity of supply: framework and instruments.

[9] The accumulation of post-marketing effectiveness (PMS) data should be a co-operative effort between companies and national, Community and international public health authorities. Facilities for the rapid sharing of these data should be in place since the information will likely have implications for all the vaccines in use in a pandemic. Appropriate mechanisms to allow collection and communication of epidemiological data on the use of pandemic influenza vaccines should be considered and developed.

8. Participants and their contributions

All Member States should commit themselves to increasing interpandemic vaccine uptake in accordance with the WHA recommendations and to taking part in the PPP which would be eligible for funding in the context of the Public Health Programme.

The contribution from industry would be a firm commitment to full cooperation in the PPP work packages developed by the public partners and work towards the speedy submission of mock-up vaccine dossiers. Industry is expected to contribute to the reduction of mortality and morbidity through shortening the time needed to produce effective pandemic vaccines.

The Commission should take all necessary steps to ensure Member States' backing to the strategy developed in this paper and the PPP in particular. It should work with the WHO to enhance the system of making available candidate influenza strains. In the research area, it should support international cooperation and the scientific outreach to Asia of the PPP. It should ensure effective input into the partnership of technical and scientific expertise, experimental and technical data from other EU research consortia working on pandemic influenza vaccine development taking into account the flexible management possibilities of integrated projects in the research area.

The Commission has agreed with the EMEA waivers of license fees to prepare the mock up dossiers. It would contact, together with the EMEA, the Federal Drugs Administration of the USA to explore the "incentive" for industry to obtain a mock-up dossier approval in the EU for non-EU markets: there is a possibility to ask for joint EMEA-FDA scientific advice, which might be useful to streamline the requirements for clinical trials.

9. WHO's role

An essential WHO role obviously would be the provision of the reference pandemic strains. It is expected that through the National Institute of Biological Standardisation and Control (NIBSC) in the UK which is part of Health Protection Agency (one of the founding partners of the PPP proposals) (the other collaborating centres in the world-wide system of influenza reference strain provision being in the USA and Japan), a determinant and authoritative link will be established. NIBSC fulfils as a WHO collaborating centre an important role in the preparation of reference strains to industry and is also involved in quality assurance schemes recently initiated by the Council of Europe's European Directorate for the Quality of Medicines, EDQM for the validation of inter pandemic clinical trial serology testing.

For the particular case of H5N1, a "library-master seed stock approach" may not provide much added value, because a H5N1 candidate vaccine (produced under a quality system), that would most likely be homologous to the pandemic H5N1-strain (if the current H5N1 situation in Asia would develop into a pandemic) has already been generated by NIBSC on Vero cells by reverse genetics and made available to Industry[10]. For the other candidate pandemic vaccine strains, such as H7, H9 and H2, a seed virus library (tested already for adventitious agents, characterisation of the virus, and in animals) is seen by WHO as very useful, if one accepts the concept of heterologous (cross-) protection. For example an 80% cross protection rate would probably be quite acceptable in case of a pandemic.

[10] Generation of influenza vaccine on Vero cells by reverse genetics: an H5N1 candidate vaccine strain produced under a quality system. Nicolson et al. Vaccine 2005, in press.

10. Financial aspects

- ***EU Public Health Programme***

The EU Public Health programme may serve as a funding for up to 60% of costs of projects that are submitted for co-funding under the annual work plans of the programme and, in exceptional circumstances for projects of high EU-value, up to 80%. Activities under the programme, that address health threats requiring a rapid response, such as those described here under the "PPP", have a total annual funding appropriation of about €16 million. Projects to implement the PPP that have as partners the vaccine institutes and public health agencies of the Member States would be considered for co-funding between the Commission and the Member States. Provided there is a positive evaluation and favourable opinion of the management committee of the public health programme, the Commission may proceed to conclude grants with the prospective beneficiaries. Support from the Member States to such PPP projects would therefore be crucial. The industry is to be involved through close association with the work of the institutes and agencies but cannot be a beneficiary. The Commission proposals for a Health and Consumer Protection Programme, tabled on 6 April 2005, contain actions which will strengthen support to the strategy put forward in this document.

- ***Solidarity and Rapid Reaction Instrument***

The Commission adopted on 6 April a proposal for a Council Regulation pursuant to Article 159 of the EC Treaty concerning the establishment of a Solidarity Fund. This proposal opens the way for reimbursement of Member States' expenditure on medicines used in public health emergencies and creates a financial framework for agreements between Member States and the pharmaceutical industry. The Solidarity Fund would allow the reimbursement of costs incurred by actual expenditures in the event of a pandemic. The fund has an annual ceiling of 1 billion € and explicitly covers costs on vaccines (and antivirals). EU Member States will be reimbursed following a proposal by the Commission and a favourable decision taken by qualified majority by the Council. For antivirals and other stockpileable medicines, reimbursement will be on the basis of the replacement of the medicines used. For vaccines, this could be on the basis of the vaccines ordered by contract by the Member States to be produced for use in the case of the pandemic, and this, therefore, could act as an important incentive for the Member States to conclude, if they so wish, advance purchase agreements with the industry.

11. Annexes

Annex : An outline of the PPP concept (26.2.2005 version)

Annex : An outline of the PPP concept (26.2.2005)

Introduction

Pandemic influenza is the greatest infectious threat to public health, and a number of vaccine companies are preparing plans to manufacture vaccine in an emergency. The programme outlined in this paper is designed to underpin these efforts by providing a library of seed stocks for vaccines against potential pandemic influenza viruses, by developing new production techniques that can be used in a wider range of facilities than traditional egg-based processes, and by assessing the protective efficacy of different vaccination regimens in animals and man.

The Health Protection Agency in the UK, the Netherlands Vaccine Institute in the Netherlands and the Statens Serum Institut in Denmark all have skills in research and manufacturing that can be combined to provide a European capability to underpin the vaccine industry in preparing for an influenza pandemic.

Background

Influenza vaccines are based around the haemagglutinin (H) and neuraminidase (N) antigens of the virus. Influenza A affects a range of animal and bird species, and 15 major H and 9 major N types have been identified. Circulating influenza strains contain one H and one N type antigen, e.g. H1N1, and there is little or no cross-protection between strains differing in these major antigen groups. New strains with different H and N antigens appear periodically (antigenic shift) and consequently cause pandemics as there is no significant immunity in the population. Major human types leading to pandemics in the last century include H1N1, H2N2, H3N2 and H3N8. Major epidemics in birds have been caused by H5N1 and H7N7, with a handful of human cases. Each type may circulate for several decades, and the surface antigens mutate slowly with time, a phenomenon called antigenic drift. As the drift between strain sub-types increases, the degree of cross-immunity afforded by vaccination or exposure falls. There is no reliable way of predicting what the next pandemic strain will be, but warning signs include the emergence of new animal strains and cross-infection to humans. A few cases of H5N1 and H7N7 have occurred in humans from infected poultry, but there has not yet been a mutation that has allowed these viruses to spread efficiently in man.

Influenza vaccines used in the inter-pandemic years are constantly updated to reflect the ongoing antigenic shift, and are trivalent, typically containing two type A strains and a type B strain. The active components are the H and N antigen proteins, which may be present as whole virions, split virions or surface antigens. The specification calls for 15 µg of each haemagglutinin per dose, and the vaccines are assessed in clinical trials by measuring the antibody response to the haemagglutinin using a haemagglutination inhibition (HAI) assay. A single dose vaccination regimen is used, and the available evidence is that this is satisfactory in a population, which has been exposed to a similar virus antigen either through natural means or prior vaccination. In the event of a new

pandemic strain the vaccine would be much less protective after a single dose, the number of poor responders depending in part on whether any of them had exposure to a similar strain and how long ago. It is assumed that for a strain such as H5N1 or H7N7 there would be little immunity from previous exposure in the population for the H antigen, but the contribution in reducing the severity of disease made by antibodies to a shared neuraminidase antigen is unknown. In practice, during a new pandemic a two-shot vaccine regimen will probably be needed until developmental vaccines with adjuvants or better antigen presentation have been proven in clinical use and are widely accepted. The vaccine industry and academia are both interested in developing regimens and adjuvants that will improve efficacy and also reduce the quantity of antigen required to allow the available production quantities to cover a wider segment of the population.

The process for deriving vaccine seed stocks is outlined in Appendix 1. At present, virtually all licensed vaccine is produced in fertile hen's eggs, but several manufacturers are working on cell culture based products. Eggs are likely to be the main source of vaccine for several years, until the low yield of cell based systems is overcome.

To deal with a potential pandemic therefore requires suitable seed stocks, made to Good Manufacturing Practice (GMP) standards, at the earliest possible time after appearance of the first cases. Manufacturers need to have sufficient capacity to produce the new vaccine, and the ability to switch from inter-pandemic vaccine strains to the pandemic strain quickly. A monovalent vaccine can be used, which will treble the number of doses available, but as each person will probably require two doses, the benefit is small. As the pandemic strain cannot be predicted, a library of potential strains for seed stocks is required, which can be drawn upon rapidly in the event of a pandemic. To obtain the maximum benefit from this the likely cross-protection for each major strain type should be investigated, along with data on the immunogenicity of the vaccine and the need for a single or double dose regimen. The programme that we are proposing covers:

11. The development and testing of a seed stock library to a stage suitable for distribution to manufacturers as a master seed lot. This library would be continually updated as new threats emerged
12. Studies on the immunogenicity of candidate vaccines in animal models first and subsequently in clinical trials using conventional haemagglutination inhibition assays. This data would form part of the model dossier required to license candidate vaccine processes under the EMEA pandemic influenza plan, and would also be used to determine the likely dosage regimen.
13. Testing of cross-protection provided by selected candidate vaccines against various wild type viruses in animal models.
14. Additional immunological studies to refine the understanding of the correlates of protection for present and future vaccines.
15. Collaboration with manufacturers through established public health networks and laboratories in the partner nations in monitoring the safety and efficacy of pandemic vaccines.

A schematic overview of the activities undertaken for pandemic vaccine development and production is outlined in Appendix 2.

The proposal envisages a partnership between the established influenza reference laboratories and public health surveillance systems of the partner nations with industry to develop and test candidate vaccines, including assistance with the setting up, monitoring and laboratory aspects of the clinical trials needed for new candidate vaccines.

Production of seed stocks

The production of seed stocks is based on a hierarchical approach, in that each potential pandemic virus strain will be assessed for its probable threat, and different stages of the seed banking process undertaken according to the perceived risk. Many new influenza strains appear each year, and undertaking GMP seed banking for them all would be impossible. Those strains believed to be a high risk would be taken through all the stages and final safety testing for release to manufacturing. A small number of strains could be then used to produce small lots for process development and clinical trials. Ideally, a partnership with a number of manufacturers would allow several candidates to be taken to clinical trials and a model dossier submitted, each based upon a different influenza strain. As the production vaccine would not be the same strain in all probability, this is unlikely to handicap a particular vaccine manufacturer, and would provide a far more solid data set on which to base future decisions on likely cross-protection and immunisation regimens.

There are five main steps to consider:

1. Setting up a definitive library of wild type influenza virus strains, continuously updated on an on-going basis.
2. Identification of potential risk strains and production of PR8 based reassortants.
3. Production of seed stock (master seed banks) of selected strains.
4. Safety testing of seed stocks in chickens and ferrets
5. Small scale production in eggs and cell culture to test a representative set of seed stocks.

Library of influenza strains

This part of the programme involves working together with the WHO collaborating laboratories in the partner nations, and in other countries to obtain new strains of influenza as they appear. Many WHO laboratories maintain their own collections, but the key part of this step is to have a single defined reference collection, verified and catalogued, for use as the basis of the seed stock programme. The expertise of the WHO centres will be used to determine which isolates are significantly different from strains already held and merit inclusion as representative strains in this collection. The collection will include representatives of all the major types and sub-types. These collections are maintained by the WHO Influenza Collaborating Centres at Mill Hill and NIBSC in the UK and National Influenza Centres in the Netherlands and France

Production of PR8 based reassortants

Representative strains from each major type will be held as PR8 based reassortants (vaccine reference strains). Where existing reference strains exist, e.g. for the H1N1 strains currently circulating, these will be held as the reference strain, but for new viruses a reassortant will be generated using reverse genetics or traditional reassortment methods. To avoid making an impossibly large collection of reassortants, strains will be selected for this stage only if they are known to cause disease in man or a relevant animal population, such as domestic birds and pigs. This concept has been welcomed by WHO, and is also suggested in the FLUSAFE proposal submitted by various parties for the FP6 research programme.

Production of seed stocks

Seed stocks will be made to GMP from a sub-set of the PR8 collection, for those strains of which there is evidence of possible human infection, either by the demonstration of antibodies in significant numbers of the exposed population as in the recent H7N7 outbreak of avian influenza in the Netherlands, or cases occurring in humans as in the H5N1 outbreaks in SE Asia. The GMP protocols will be checked with participating manufacturers to ensure that the product is compatible with existing

processes. The process consists of serial passage (usually in eggs) of the reference strain to make a master seed bank, commonly around passage 10 or 11. Strains which have been safety tested can be produced in level 2+ containment, but new strains have to be handled at level 3 until safety testing is complete. Safety testing can be performed in parallel to save time in an emergency. Prior production of seed stocks could save up to 1 month in an emergency, and individual vaccine manufacturers have welcomed this concept. Collectively, the European Vaccine Manufacturers have stated recently that they do not see a significant time saving, which is at odds with their previous and separate opinions.

Safety testing of seed stocks

Influenza PR8 reassortants are tested for safety (i.e. infectivity for humans and animals) before they can be released using a standard protocol of challenging chickens and ferrets. Seed banked stocks will be tested in this way if they are to be used in production or distributed beyond the producing facility, although the timing of this work will depend upon the urgency (see above).

Small scale production to GMP

A small number of seed stocks will be tested in representative egg and cell culture systems to determine their suitability for production. Strains will be selected for small scale production testing if there is evidence of human cases occurring (e.g. H5N1). Testing in specific cell culture systems would require collaboration with manufacturers to transfer protocols, or could be undertaken by manufacturers themselves.

Liaison with industry

Seed banks will be prepared by the public partners using industry standard protocols, and small scale production can also be undertaken by these partners or by industry directly.

Testing candidate vaccines for protection in animal models

To investigate the degree of cross protection of seed stocks and existing vaccine candidates against relevant wild type strains, a small number of vaccine strains will be tested for protection in animal models. The ferret model of influenza is well established and is believed to correlate well with human disease, using fever and viral load in lung washes as indicators of infection. Carefully designed experiments will enable the effect of different previous exposures, e.g. to H1N1, to be determined when combined with vaccination by a single or two-shot regimen of a new vaccine (e.g. H5N1) against a challenge with a wild type virus (in this example H5N1). It will also allow the protective efficacy of stockpiled vaccine such as the H5N1 candidates being made in some countries, to be tested against new strains of the same main type when they emerge, either giving reassurance or prompting work on developing a new vaccine seed.

Immunological testing to prove efficacy in humans

The classical method of predicting the efficacy of an influenza vaccine is by measuring the antibody response in humans to the HA antigen. The current criteria for interpandemic influenza vaccines are based on these assays and laid down in regulations by the European Committee for Proprietary Medicinal Products (Table 1). Fulfilment of these criteria is a requirement for annual registration of interpandemic influenza vaccines in the European Union.[1] In general, hemagglutination inhibition (HI) antibody titers $\geq$ 1:40 are considered to be protective. The efficacy of the influenza vaccine is estimated to be between 70 and 90% in young healthy adults.

[1] CPMP/BWP/214/96. September 1996; Circulaire No 96-0661 : 1 – 22.

Table 1. Registration criteria for interpandemic influenza vaccines.

Immunogenicity criteria	Age group	
	18 – 60 years	> 60 years
Seroconversion in HI titers	>40%	>30%
Mean fold increase in HI titres prevaccination to post-vaccination	>2.5	>2.0
Post-vaccination titres of ≥ 1:40	>70%	>60%

Seroconversion: ≥ 4-fold increase in HI titre to a titre of ≥1:40. Mean fold increase in HI titres are measured before and at day 21 after vaccination.

However, it is well known that there is no clear correlation between HI titers and protection. Thus the use of HI titers to predict efficacy of a vaccine, especially a pandemic vaccine, is a risky policy. There is a clear need to establish an immune response that is a reliable predictor of vaccine efficacy.

Testing vaccines for protection in humans

For determining parameters that predict the efficacy of a pandemic vaccine, several trials need to be performed:

1. General set-up of trials in man
2. Trials in man for licensing
3. Trials in man using a candidate pandemic vaccine
4. Determining cross-protection of the existing seed lots to the circulating pandemic strain
5. Determining correlates of protection
6. Post Marketing Surveillance.

A detailed description on the objectives of these trials and the results aimed for is outlined in Appendix 3.

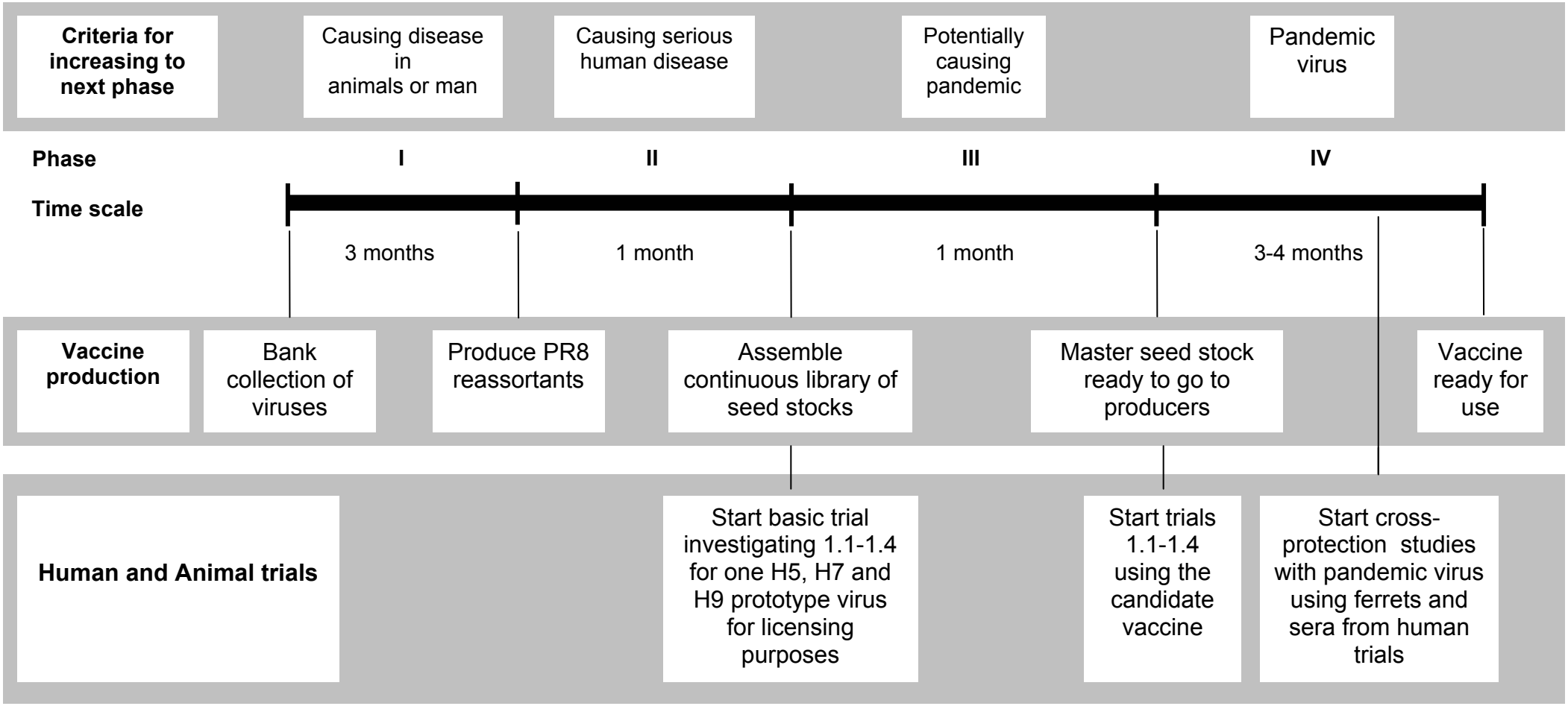
Appendix 1: Current procedures for influenza vaccine

Influenza vaccine is prepared as inactivated whole virions of influenza virus, or as an antigen fraction from the virus (split virion vaccines). The virus is grown in eggs, or occasionally in cell culture, and concentrated by centrifugation or chromatography. The inactivated or extracted material is then standardised and processed as the finished vaccine which is tested for safety and antigenicity.

As influenza is constantly evolving the antigenic composition of the vaccine is changed each year. Normally, WHO through its collaborating centres (NIBSC in the UK) provide a vaccine reference strain that is believed to contain the antigens most likely to give protection during the next influenza season. Three separate strains are normally issued to make trivalent vaccine. This is grown in eggs to provide master and working seed stocks, which are used for producing the final virus cultures for the vaccine. For several decades reassorted strains have been issued for preparation as the seed stock, optimised to grow in eggs to high titre and to express the necessary antigens. Essentially, standard base virus (PR8) which has low virulence is used as the base and the appropriate H and N antigens are added to this virus by reassortment. This can be done by infecting eggs with both the PR8 virus and the wild type virus containing the antigens, and isolating the progeny displaying the correct characteristics. In the last five years, a reverse genetics process has been developed allowing reference strains to be produced by genetic modification. The reference strains, reassorted or reverse genetics, are designed and tested to be apathogenic for humans so that vaccine can be produced in containment level 2 facilities. They are usually prepared in the previous season and validated to be ready for the annual vaccine production, and would not be available immediately in a new outbreak, as it takes 2 months to derive and safety test them.

Each year, the new vaccine is tested in animal and clinical trials for safety and immunogenicity, including the production of neutralising antibodies against the relevant influenza strains. This takes several months, and the total time taken to produce each vaccine is nearly a year, which is far too long to be of use in an epidemic of a new influenza strain.

Appendix 2: Vaccine production for Pandemic influenza



Appendix 3: Testing vaccines for protection in humans

For determining parameters that predict the efficacy of a pandemic vaccine, several activities are needed.

1. General set-up of trials in man

Immunogenicity of the candidate pandemic vaccine will be initially determined based on HI antibody titers. To this end the registration criteria for interpandemic vaccines, as depicted in Table 1 will be applied. The trials will be set-up as a prospective, observer-blind, parallel-group, randomised, multi-center study comparing the pandemic vaccine and a placebo. The trials will be performed in research institutions of several EU-members, involving The Netherlands, UK and Denmark. Several issues need to be investigated, which are specific for the degree of immunogenicity of a pandemic influenza vaccine. The vaccine is to be used in a background of low cross-reactive immunity in the susceptible population and will be preferentially administered in low dose to increase the number of people that can be vaccinated. Therefore, several trials need to be performed using a candidate vaccine or candidate vaccines that contain HA antigens of influenza viruses that are likely to cause an outbreak of pandemic influenza. These investigations are performed at the moment master seed stocks are prepared for large-scale production. The trials will be performed with 200 persons per group and several groups per trial.

1.1 Dose – response trial using a single vaccination. This trial will be used for optimalisation of the vaccine dose.
1.2 Dose – response trail using a single vaccination in combination with various adjuvants.
1.3 Dose – response trial using two doses. This trial will be necessary if the aforementioned trials do not indicate induction of protective immunity.
1.4 Dose – response trial in young children, below 9 years of age and in elderly above 65 years of age. This trial is indicated as people in these age-groups may respond differently to vaccination as compared to healthy human adults.

2. Trials in man for licensing

For each HA serogroup that is present in the continuous library of seed stocks, these dose – response trials need to be investigated at least once to determine general immunogenetic characteristics in this serogroup. Data from these trials will be used for licensing purposes.

3. Trials in man using a candidate pandemic vaccine

In case of a threatening outbreak cross-protection studies will need to be performed to evaluate the potential protective immunity induced by the candidate vaccine to the circulating potential pandemic virus. To this end, HI studies and microneutralisation tests are performed in ferrets (see above) and using sera of people vaccinated according to the optimised protocol (see 1) and using the circulating virus as target. These studies will indicate which vaccination protocol under 1.1 – 1.4 is sufficient for inducing cross-protective HI titers. Data from these experiments will indicate which vaccination regimen with the candidate vaccine is likely to induce protection for the pandemic virus, or whether a new vaccine seed needs to be developed as depicted under 4.

4. Determining cross-protection of the existing seed lots to the circulating pandemic strain.

In case of a pandemic outbreak, parallel to the production of vaccine using the pre-defined, non-homologous vaccine virus, a new vaccine is generated based on the circulating pandemic virus (See Appendix 2). This two-track approach is based on the available seed lot to reduce time (track 1, 3-4 months for making vaccines from a master seed stock) and the second track starting as soon as a pandemic appears to emerge (track 2, 7-8 months for making vaccines based on the circulating virus). Cross-protection studies in track 1 will predict the efficacy of the candidate vaccine from the master stocks against the pandemic virus and will allow the decision to go ahead or switch to track 2 entirely. In track 2, matching of the circulating pandemic virus to the improved vaccine can be obtained by introducing the pandemic HA and NA (possibly mutagenized by removing virulence factors) in the PR8 backbone, as described before. Probably this will double the production time from 4 (in the case of track 1) to 8 months (in the case of track 2). Modelling may indicate how this would affect mortality and morbidity data, by using estimates of pandemic impact in situations where vaccines are available after 4 and 8 months and where the four month vaccine has different levels of protection.

5. Determining correlates of protection

Correlates of protection will be established to refine our understanding of the immunological basis of efficacy of present and future influenza vaccines. In addition to the classical correlates as described in Table 1, other immunological parameters such as antibody titers specific for neuraminidase and the matrix protein, IgA concentrations in nasal wash fluid, and markers for cell mediated immunity will be established. The levels of these and the classical parameters are identified in people vaccinated with different vaccines and representing different age groups and will be correlated to protection from disease.

6. Post Marketing Surveillance

We will provide assays, support and surveillance for assistance of vaccine manufacturers in post marketing surveillance (PMS). We offer technology for passive and active surveillance of disease. As part of the project we can set up the infrastructure to monitor and improve the efficacy of protection.