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6 Public Health Response: Vaccines

6.1 Introduction

Ideally, vaccination would be the primary public health response in the event of an influenza pandemic. However, a pandemic vaccine can only be developed once the pandemic virus is identified and the first vaccine doses will only begin to appear four to six months after that. The first pandemic wave may well have passed before a pandemic vaccine becomes available.

This chapter outlines the benefits of seasonal influenza and pneumococcal vaccination, and how maximising uptake in target groups now will aid pandemic preparedness. It explains how vaccines are produced and supplied in the inter-pandemic and pandemic period. It outlines current vaccine priority groups for pandemic vaccine and also describes the rationale and plans for procurement of A/H5N1 vaccine for essential healthcare and other workers.

6.2 Global Vaccine Action Plan

Current world manufacturing capacity of influenza vaccine covers just 5% of the world's population. In September 2006 the WHO published a Global Vaccine Action Plan with strategies aimed at increasing influenza vaccine production and surge capacity before and during an influenza pandemic.[(1)] Three main approaches were identified: a) an increase in seasonal vaccine use; b) an increase in production capacity; and c) further research and development. It will not be possible to bridge the expected gap between vaccine demand and supply in the short term. Implementation of the Action Plan will require a sustained global effort and commitment by countries, the vaccine industry, the research community and donors over a period of five to ten years.

6.3 Benefits of seasonal vaccination

In the inter-pandemic period, influenza vaccination remains the most effective way to reduce the impact of influenza, especially in high-risk groups. This requires annual vaccination with the current recommended strains, as advised by WHO.

Vaccination is recommended for two groups of individuals[2]:

- Any individual older than six months of age who is at increased risk of influenza related complications
- Those at increased risk of transmitting influenza to a person at high risk for influenza complications.

The high-risk groups are adults and children with any of the following:

- Chronic illness requiring regular medical follow-up (e.g. chronic respiratory disease, including cystic fibrosis, moderate or severe asthma, chronic heart disease, bronchopulmonary dysplasia, diabetes mellitus, Haemoglobinopathies, chronic renal failure etc.)
- Immunosuppression due to disease or treatment, including asplenia or splenic dysfunction
- Persons aged 50 years or older, as recommended by WHO
- Children on long term aspirin therapy (because of the risk of Reyes Syndrome)
- Children with any condition (e.g. cognitive dysfunction, spinal cord injury, seizure disorder, or other neuromuscular disorder) that can compromise respiratory function
- Residents of nursing homes, old peoples' homes, and other long stay facilities where rapid spread is likely to follow the introduction of infection.

Vaccines that are well matched to the current circulating strains are 70-90% effective in preventing illness in healthy adult volunteers.[3] Annual vaccination offered to all older people, irrespective of whether they have any underlying disease, is cost effective.[4-6] Influenza vaccine has been shown to prevent severe complications and death due to influenza in elderly nursing home residents. Hospitalisation rates, cases of pneumonia and respiratory illness and death rates were reduced by over 50% in one elderly residential population that had been vaccinated.[7] The vaccine is also effective in

reducing mortality in older people living in the community and those who are not classed as high risk.[4-6]

The ideal time for vaccination in the Northern Hemisphere is from September to mid-October as influenza activity increases from October onwards. On average, it takes two weeks for the vaccine to induce a protective antibody response.

Increasing seasonal vaccination uptake is important not only for reducing the impact of influenza each year, but also as it increases vaccine production capacity, for increasing the capacity to respond when a pandemic strain is detected. In addition it improves national capacity and experience in implementing vaccination programmes. It also fosters increased familiarity with and public confidence in influenza vaccines. The aim is to increase uptake in all high-risk populations with a target of 75% uptake in older people by 2010.[8]

In this context, the National Immunisation Advisory Committee (NIAC) has recommended the extension of routine influenza vaccination to everyone aged 50 years and over on a phased basis.

The Expert Group advises that every effort should be made to increase seasonal vaccination coverage of all people at high risk in all settings, (e.g. healthcare clinics, GP surgeries and workplaces), and to achieve the WHO target of 75% uptake of seasonal vaccination by older people by 2010.

6.4 Inter-pandemic vaccine production and supply

During the inter-pandemic period, trivalent influenza vaccine is manufactured according to WHO recommendations released in February each year for the Northern Hemisphere. Suitable seed viruses that grow well in eggs are identified and developed. Vaccine viruses are grown in embryonated hens' eggs and the infected allantoic fluid is then harvested. The viruses are purified, inactivated and further treated to produce either a whole virus, split or

subunit virus. The lead-time for vaccine production is approximately six months. Vaccines for human use are not manufactured in Ireland.

6.5 Pandemic vaccine production and supply

At the beginning of a pandemic, a vaccine whose efficacy and safety are clearly established will not be available against the pandemic virus strain. The vaccine needs to match the unique genetic and antigenic characteristics of the pandemic virus strain, and will need to be developed once the pandemic strain has been recognised. Following a lead-time of at least four to six months to produce the first doses of vaccine, the subsequent increase in supply will be progressive. It is unlikely that pandemic-specific vaccine will be available before the end of the first pandemic wave.

There are a number of rate limiting steps involved in the manufacturing process, not least the ability to develop seed viruses in a timely fashion. Other difficulties include the availability of fertilised hen's eggs, and the growth rate of the virus in hen's eggs, especially if the pandemic occurs outside of the usual production season.

6.6 Advance Purchase Agreement for pandemic vaccine

The Global Vaccine Action Plan notes that countries may be required to pay for under-used capacity to assure that sufficient pandemic vaccine doses are produced within the required time frame. This is the rationale behind the advance purchase agreements (or sleeping contracts), which a number of countries are making with vaccine manufacturers. **The Expert Group has advised that Ireland should take this approach and provide for the purchase of sufficient pandemic vaccine to vaccinate the whole population, in the event of a pandemic emerging.**

6.7 Research and development

The third approach in the Global Vaccine Action Plan focuses on efforts being undertaken by researchers, including the vaccine industry, to design more potent and effective vaccines that: a) are capable of inducing protective

responses after one dose, and/or b) induce broad spectrum and long-standing immunity against both seasonal and pandemic influenza strains.

Investigation continues into the best method of delivering the vaccine during a pandemic and studies are being undertaken to define the formulation and dosage regimens that will make the best possible use of available vaccine antigen at the time of a pandemic.

Recent experience with H5N1 vaccine trials indicate that split-product or sub-unit vaccines (the types in use in the EU as seasonal influenza vaccines) are likely to require very high doses of haemagglutinin antigen per dose (90µg) without an adjuvant, 30µg or more if using alum adjuvant, but potentially in the range of 3.8 – 7.5µg if newer adjuvants are used. Data from a whole virus non-adjuvented vaccine (using wild-type H5N1 strain and grown in ell culture) suggest that 7.5µg will be needed.[9]

Presently it is assumed that in the pandemic all those vaccinated will lack previous exposure and will require two doses of vaccine, three weeks apart to confer maximum protection.[10]

6.8 Pandemic vaccine licensing

The new vaccine will be licensed centrally within Europe on the recommendation of the European Medicines Evaluation Agency (EMEA).

As already outlined, at the beginning of a pandemic, no vaccine will be available whose efficacy and safety is clinically established against the pandemic strain. In order to cater for the urgency of the situation and in the interests of public health, it may be necessary for the EMEA to recommend the granting of a marketing authorisation on the basis of less than complete data but subject to specific obligations to subsequently complete the data. This type of an authorisation is called a “conditional marketing authorisation” (CMA).

A conditional marketing authorisation may be granted where:

1. The risk-benefit balance of the vaccine is positive;
2. It is likely that the applicant will be in a position to provide comprehensive clinical data;
3. Unmet medical needs will be fulfilled;
4. The benefit to public health of the immediate availability of the vaccine outweighs the risk inherent in the fact that additional data are still required.

The authorisation is not intended to remain conditional indefinitely.

To date the European Medicines Evaluation Agency (EMEA) has approved marketing authorisations for two human pandemic influenza vaccines using a 'core dossier' approach – Focetria and Daronrix. This is a novel European approach that is intended to speed up the eventual process for obtaining an authorisation for a pandemic vaccine. It allows the submission, before the outbreak of a pandemic, of a core pandemic vaccine dossier based on a "mock-up" vaccine containing a pandemic influenza candidate virus. This mock-up vaccine can be evaluated and a Marketing Authorisation granted before a pandemic. In an officially declared pandemic situation (WHO Phase 6), the pandemic vaccine would be approved for use following a variation, which will contain only the quality data specific to strain replacement.

In 2005 the EMEA introduced a number of incentives to encourage companies to use the core dossier approach. These include a commitment of the Agency's Committee for Medicinal Products for Human Use (CHMP) to accelerate the scientific evaluation of applications for scientific advice and marketing authorisations for pandemic vaccines 'core dossiers'. Work on pandemic influenza preparedness began in 2003 and the EMEA issued its draft pandemic crisis management plan in 2005 for public consultation. The

plan aims to establish efficient procedures for the assessment and authorisation of pandemic vaccines via the centralised procedure and for the surveillance of vaccines and antiviral medicines used in a potential pandemic.

6.9 Pandemic vaccine administration

The Expert Group advises that a mechanism for the storage, distribution and administration of pandemic vaccine should be developed as part of the planning response.

Childhood immunisation is an extremely beneficial and cost effective public health intervention. Interruption to the delivery of routine scheduled immunisation could lead to children's health being put at risk.

The Expert Group advises that the primary childhood immunisation programme should continue during a pandemic unless clinical circumstances dictate otherwise.

6.10 Expert Group advice on pandemic vaccine priority groups

WHO has advised countries to set goals and priorities for the use of vaccines during a pandemic. These goals should reflect the particular circumstances of each country.

Priorities on who should receive influenza vaccination during a pandemic may differ from interpandemic recommendations as follows:

- The target population for vaccination will extend beyond the typical high-risk groups;
- Simultaneous occurrence of disease and vaccination programme.
- Limitations set by the availability and quantity of vaccine will determine who receives the vaccine initially.
- Vaccine will need to be distributed and administered as rapidly as possible in a much shorter timeframe
- It is likely that there may be no vaccine available during the first wave of the pandemic, and in the second wave there may be vaccine shortages

In prioritising target groups for vaccination, the Expert Group advises that the goals for Ireland in a pandemic should be as follows:

- **To prevent or reduce deaths and hospital admissions due to influenza**
- **To prevent and reduce influenza related morbidity**
- **To maintain essential services by protecting the health of essential service workers.**

In order to address the first two goals, the epidemiology of the particular novel virus, including information on who is most frequently affected, the clinical severity of the disease and the age specific mortality rates will be used to help determine who the priority groups for early vaccination should be. In addition, it is likely that WHO will give advice on priority groups for immunisation.

The Expert Group advises that the following population sub-groups are prioritised to receive initial supplies of the pandemic virus vaccine:

Priority groups for vaccination during an influenza pandemic

1. Healthcare staff with patient contact (including ambulance staff) and staff in residential care homes for the elderly
2. Providers of essential services e.g. fire, utilities, Gardaí, security, communications, defence forces, undertakers, and essential healthcare staff without direct patient contact
3. Those with high medical risk e.g. chronic respiratory or heart disease, renal failure, diabetes or immunosuppression due to disease or treatment, women in the last trimester of pregnancy, and children aged from 6 months to 23 months
4. All over 65 years of age
5. Selected industries – maintenance of essential supplies e.g. pharmaceuticals
6. Selected age groups, depending on advice from WHO e.g. children
7. Offer to all

Please note that these priorities are subject to change as the epidemiology becomes evident.

6.11 Surveillance of pandemic vaccination

6.11.1 Vaccine effectiveness

There will be at best limited data on efficacy of the pandemic vaccines in advance of their use. Therefore their effectiveness in the field will need to be assessed rapidly. This may be done by comparing rates of influenza like illness, hospitalisation, and/or death among vaccinated and unvaccinated persons, and by vaccine product.

The Expert Group advises that protocols for timely assessment of vaccine effectiveness should be drawn up in advance of a pandemic.

6.11.2 Vaccine uptake

Once the priority groups for vaccination have been identified the denominator populations of these groups will need to be determined to allow uptake targets to be established, and progress towards achieving them to be monitored. This presents a logistical challenge, given the limitations in current systems for monitoring vaccination uptake, and the lack of chronic disease registers and universal primary care registration.

Influenza vaccine uptake is currently measured using GMS data based on returns by GPs to the HSE Primary Care Reimbursement Service, allowing measurement among only those patients in the population with a GMS card i.e. all patients over 70 years but only 50% of the population aged 65 – 69 years. There is no routine way of measuring uptake in at risk populations less than 65 years old at present. Therefore measurement of vaccine uptake during a pandemic will be very difficult.

The Expert Group advises that options for measuring vaccine uptake among priority groups and generally should be examined as part of the planning process.

6.12 Monitoring adverse events related to vaccination

Safety is critical for pandemic vaccines for the following reasons:

- Vaccination of the whole population (different age groups, risk groups, pregnant women);
- Unknown safety profile;
- Concomitant disease;
- Public confidence in the vaccination programme can only be maintained by the perception that competent authorities will rapidly and adequately assess the safety of vaccines;
- Communication of safety is essential to respond to public concerns, starting in the inter-pandemic phase.

The Irish Medicines Board (IMB) is the regulatory body for human and veterinary medicines in Ireland and is the national competent authority under EU Regulations and Directives. One of its main roles is pharmacovigilance and drugs safety monitoring. Of particular importance are all suspected reactions to newly authorised products, serious reactions to established products and suspected reactions to vaccines or medicines in pregnancy.

The EMEA received a proposal from EVM (European Vaccine Manufacturers) for a pharmacovigilance plan for pandemic vaccines, to which the Agency's Pharmacovigilance Working Party (PhVWP) responded in December 2005. In its response, the PhVWP discussed four major requirements of such a pharmacovigilance plan:

- Routine pharmacovigilance activites (spontaneous reporting of adverse drug reactions (ADRs), with a focus on severe ADRs to enable signal detection)
- Additional pharmacovigilance activities i.e. prospective cohort study of an adequate number of vaccines.

- Shared responsibilities of companies and competent authorities in risk management.
- Feasibility – adequate tools should be in place to handle the enormous workload.

It is envisaged that there will be a harmonised approach of risk management by vaccine manufacturers.

The IMB will monitor adverse events related to vaccination with pandemic vaccine. During the pandemic, the IMB will produce regular reports on vaccine safety. The IMB may direct changes in the vaccine, the vaccination schedule or the program during the pandemic in response to immunogenicity, effectiveness and safety data received during the pandemic.

6.13 H5N1 Vaccines

6.13.1 Potential benefit of stockpiling H5N1 vaccines

A/H5N1, which has caused unprecedented outbreaks in poultry in Southeast Asia since late 2003, and more recently in Europe and Africa, could be the source of the next pandemic, in other words, the next pandemic virus strain may originate from A/H5N1.

WHO has told Member States that, for affluent countries, stockpiling vaccines against H5N1 may be a viable option.(1) It may offer some protection against a future human pandemic strain for healthcare and other essential workers pending development of the precisely matched pandemic strain vaccine. If however a future pandemic strain diverges significantly from this strain, then the H5N1 vaccine will not match the pandemic strain, and it would be ineffective. This is the rationale behind the EMEA's 'core dossier' approach as previously discussed. Further opportunities exist, however, with use of A/H5N1 pre-pandemic or 'mock-up' vaccines as follows:

- Allows the establishment of a collaborative approach between stakeholders including public health, industry, regulatory agencies and clinical service providers, in advance of a pandemic.

- Allows the exploration of likely scenarios in a mass vaccination program.

- Allows for the development of pharmacovigilance systems for a medicinal product with limited clinical data before market authorisation

6.13.2 Pre-Pandemic Vaccination

In August 2007, the European Centre for Disease Prevention and Control published two Technical Reports produced by Expert Advisory Groups on Human H5N1 Vaccines - the first dealing with scientific questions and the second dealing with public health and operational questions.(9;11) The purpose of these reports is to create a common understanding of the scientific and public health rationale for these vaccines. The reports were presented at the 4th Joint EC/ECDC/WHO Workshop on Pandemic Influenza Preparedness in September 2007.(12)

The Expert Group on Scientific Questions found that the data on the developmental H5N1 vaccines are promising with regard to cross-protection and cross-reactivity *provided* the pandemic virus is a H5 strain. However if the next pandemic arises from a non –H5 subtype, a H5N1 vaccine will offer no protection. Modelling data does suggest that public health benefits from an appropriate vaccine given before the pandemic, even if poorly matched to the pandemic strain, will be greater than from a vaccine of much higher efficacy, but not widely available until after a pandemic is underway.

The Public Health Expert Group notes that the group that would most benefit from vaccination with an H5N1 vaccine will change with the evolving profile of the developing pandemic and also depend on the timing and use of the vaccine. Should infection of domestic birds with H5N1 become more widespread in Europe, while remaining predominantly an animal infection, it would be reasonable to consider poultry workers and veterinarians for vaccination with an H5N1 vaccine. However, if the situation develops so that

human-to-human transmission becomes more important poultry workers and veterinarians would probably no longer be a priority.
The four groups that were considered for targeted use of H5N1 vaccine and the rationale for this are:

1. Healthcare workers and laboratory staff – more likely to be exposed
2. Social care and other "front-line" staff (having face to face contact with the public) – more likely to be exposed.
3. Vulnerable populations (similar to those currently recommended for seasonal vaccine, i.e. the elderly, those with chronic medical conditions) – can be anticipated to be especially vulnerable.
4. Children – may be the most potent spreaders of influenza in the community and vaccinating them may influence the size and duration of the pandemic.

There are epidemiological and ethical considerations regarding all of these groups which need to be examined further.

The report also states that an H5N1 vaccine should not be administered to any large population groups prior to the emergence of a H5 –based pandemic. Early vaccination is scientifically reasonable, but this has to be balanced against logistic, economic and political considerations. Substantial continuous investment (in order of tenths of 1% of GDP) is needed in order to reduce the impact of a pandemic through H5N1 vaccines, but this may be cost effective if an H5N1 pandemic does occur.

6.13.3 Recommendations for use of H5N1 vaccine

There is scientific data published that demonstrates that H5N1 vaccines can induce immunity and provide cross protection against clades/subclades of circulating strains. In addition, modelling data shows that even a poorly matched pre-pandemic vaccine of limited effectiveness (20%) could have a significant impact on size, duration and morbidity and mortality during a H5 derived pandemic. **The Expert Group advises that the Department of**

Health and Children considers commissioning a cost-benefit analysis looking at various options for use of pre-pandemic H5N1 vaccine.

The Expert Group advised in August 2005 that a limited amount of H5N1 vaccine should be stockpiled to provide for vaccination of healthcare and other essential workers. This advice was accepted by the Minister for Health and Children.

The priority groups recommended for H5N1 vaccine were:

Priority Group 1: Healthcare staff, with direct patient contact (including ambulance staff) and staff in residential care homes for the elderly

Priority Group 2: Providers of essential services e.g. fire, utilities, Gardaí, security, communications, armed forces, undertakers, and essential healthcare staff, without direct patient contact.

Health care workers with direct patient contact are defined as:

> *Persons who provide or assist in provision of direct health care (within 1 metre) to potential or known influenza cases with or without personal protective equipment*.

The Expert Group will advise on use of this vaccine when the pandemic is declared. Recommendations regarding priority groups will also be kept under review.

6.14 Pneumococcal vaccination in the pandemic alert period

Streptococcus pneumoniae is one of the main pathogens responsible for secondary bacterial infection following influenza infection, especially in the elderly or those who have underlying medical conditions. The vaccine is currently recommended for use in persons who are at increased risk of pneumococcal disease and its complications, particularly those with[13]:

- Asplenia or splenic dysfunction including surgical splenectomy sickle cell disease and coeliac syndrome

- Chronic renal disease or nephrotic syndrome
- Chronic heart, lung or liver disease, including cirrhosis
- Diabetes mellitus
- Complement deficiency (particularly early component deficiencies C1, C2, C3, C4)Immunosuppressive conditions (e.g. some B- and T-cell disorders, HIV infection, leukaemia, lymphoma, Hodgkin's disease) and those receiving immunosuppressive therapies CSF leaks, either congenital or complicating skull fracture or neurosurgery
- Intracranial shunt
- Candidate for, or recipient of a cochlear implant
- Persons aged 65 years of age and older
- Children < five years of age with history of invasive pneumococcal disease, irrespective of vaccine history

Increased use of pneumococcal vaccine in the pandemic alert period may decrease rates of secondary bacterial infections during a pandemic. Because large-scale pneumococcal vaccination might not be feasible once a pandemic occurs, the pandemic alert period is the ideal time to promote and deliver this preventive measure.

The Expert Group advises that the benefits of pneumococcal vaccine for at risk groups should be promoted among at risk groups and healthcare professionals.

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