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Vaccination strategies against pandemic (H1N1) 2009

accompanying the

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Pandemic (H1N1) 2009

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INTRODUCTION

In April 2009, a novel strain of a human influenza A(H1N1) virus was identified that had caused illness in Mexico and the United States first, in March and April 2009.

On 11 June 2009, the World Health Organisation (WHO) declared a pandemic, caused by the novel influenza A(H1N1) virus, hereafter called 'pandemic (H1N1) 2009 influenza virus'. This declaration was in line with WHO's global influenza preparedness plan where phase 6, the pandemic phase, is defined as the virus causing sustained community-level outbreaks in at least two countries in one WHO region and in at least one other country in a different WHO region. The declaration therefore reflected the spread of the new virus, not the severity of illness caused by it.

Current experience is that some 'higher risk' groups are more likely to suffer severe illness if infected (people with underlying chronic conditions[1], pregnant women and young children). Most patients have suffered only a mild, self-limiting illness and the health services have generally coped.

Notwithstanding the moderate symptoms caused by the pandemic (H1N1) 2009 influenza virus so far, the wide spread of the virus poses a potentially serious threat. In the winter ahead, the virus could transmit more easily and there will be more other respiratory infections than in summer. In addition, it cannot be ruled out that the pandemic (H1N1) 2009 influenza virus might mutate or exchange genetic material with other influenza viruses, which could lead to it causing a more severe illness.

Vaccines play an important role in the preparations for the increase in infections by the pandemic (H1N1) 2009 influenza virus expected from the autumn onwards. Indeed, vaccination with a pandemic vaccine effective against the pandemic (H1N1) 2009 influenza virus can be considered as one of the most effective public health measures in that it both offers protection to the individual and prevents onward transmission. Obviously, the public health response should not rely on vaccination alone but should also include other public health measures, both pharmaceutical (e.g. antivirals) and non-pharmaceutical (e.g. social distancing or personal protective equipment).

As specific vaccines cannot be developed until the pandemic influenza strain has been isolated, the vaccine will initially be available in only limited quantities and demand may initially be higher than supply. In addition, the yield of pandemic (H1N1) 2009 influenza antigen to produce vaccines might be lower than the yield usually seen for seasonal influenza strains, which, in turn, would limit supply. The initial limited availability of vaccines, together with the potential need for a large-scale vaccination campaign, poses challenges to healthcare systems and highlights the need for a carefully planned vaccination strategy.

This Commission Staff Working Document outlines a possible vaccination strategy based on the evidence currently available, while recognising that the responsibility for developing a vaccination strategy against pandemic (H1N1) 2009 lies with the Member States. Therefore,

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[1] E.g. chronic respiratory diseases; chronic cardiovascular diseases, excluding isolated mild hypertension; chronic metabolic disorders, notably diabetes; chronic renal and hepatic diseases; persons with congenital or acquired immunodeficiency; chronic neurological or neuromuscular conditions.

Member States may develop different vaccination strategies, taking into account their epidemiology, health service structures and available resources. It should also be stressed that any vaccination strategy might need to be adapted as more epidemiological, clinical and pharmaceutical evidence becomes available and as the pandemic progresses. Vaccination strategies against pandemic (H1N1) 2009 will therefore need to be reviewed regularly.

1. POSSIBLE OBJECTIVES OF VACCINATION

On 7 July 2009, the WHO Strategic Advisory Group of Experts (SAGE) on Immunisation identified three objectives that countries could adopt as part of their pandemic vaccination strategy:

- protect the integrity of the healthcare system and the country's critical infrastructure, i.e. maintain essential services;
- reduce morbidity and mortality, i.e. protect the vulnerable;
- reduce transmission of the pandemic virus within communities, i.e. limit the speed of spread of infection and limit the burden on the healthcare system.

The categories of people who would be covered by those three objectives are listed in Table1.

Table 1. Rough estimates[2] of the numbers of EU citizens who would be covered by the three objectives identified by SAGE

	Population	% of the whole population
Objective: maintain essential services (approximately 6 %)		
Healthcare workers	10,000,000	2 %
Workers in other essential services	20,000,000	4 %
Subtotal	**30,000,000**	**6 %**
Objective: protect the vulnerable (approximately 29 %)		
Very young children (0-24 months)	10,000,000	2 %
Persons aged between 25 months and 64 years with underlying chronic conditions increasing the risk of severe disease	40,000,000	8 %
Pregnant women	7,500,000	1.5 %
People aged 65 and older	85,000,000	17 %
Subtotal	**142,500,000**	**28.5 %**

[2] Note: percentages have been rounded, so the subtotals do not add up exactly.

Objective: limit the speed of spread of infection and the burden on the healthcare system (approximately 65 %)		
Healthy children and adolescents aged between 25 months and 18 years	85,000,000	17 %
Healthy adults not included in the previous groups	240,000,000	48 %
Subtotal	**325,000,000**	**65 %**
Total population (EU27)	***500,000,000***	***100.0 %***

1.1. Maintaining essential services

During a pandemic, there is likely to be a degree of absenteeism from work. In the United Kingdom, it has been estimated that 12 % of the adult population will be off work at the peak of the pandemic[3]. A survey led by researchers at the Johns Hopkins Bloomberg School of Public Health found that approximately one in six public health workers (approximately 16 %) said they would not report to work during an influenza pandemic, regardless of its severity[4].

Organisations will need to assess, in their business continuity plans, whether such levels of absenteeism would be disruptive to their activities. This applies, in particular, to organisations which deliver services essential to keep society working. Examples include but are not limited to:

- Healthcare workers;
- People working in command and control centres and in essential services such as (in no specific order):
    - electronic communications;
    - security (law and order);
    - civil protection services and other first responders;
    - electricity production and distribution;
    - water supply;
    - food production and distribution (including transport);
    - oil and gas recovery, processing and distribution (including transport);
    - public transport systems;

3 http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_102892.

4 Barnett, D.J., Balicer, R.D., Thompson, C.B., Storey, J.D., Omer, S.B. et al., 2009 Assessment of Local Public Health Workers' Willingness to Respond to Pandemic Influenza through Application of the Extended Parallel Process Model. PLoS ONE 4(7): e6365. doi:10.1371/journal.pone.0006365.

- financial and logistics services.

Essential services might need to be targeted for vaccination against pandemic (H1N1) 2009 influenza, especially those where the estimated levels of absenteeism would disrupt operation of the service. This applies, in particular, to healthcare workers who, in addition, will have to cope with far higher numbers of patients than usual.

1.2. Protecting the vulnerable

According to the current evidence on pandemic (H1N1) 2009, the following population groups are considered at higher risk of severe pandemic (H1N1) 2009 influenza infection than the general population:

- people with underlying chronic conditions increasing the risk for severe disease (e.g. chronic respiratory diseases; chronic cardiovascular diseases, excluding isolated mild hypertension; chronic metabolic disorders, notably diabetes; chronic renal and hepatic diseases; persons with congenital or acquired immunodeficiency; chronic neurological or neuromuscular conditions.),

- young children (especially those aged 0 – 24 months),

- pregnant women.

Details of the evidence of the risk of people developing severe disease when infected with the pandemic (H1N1) 2009 influenza virus are available in the European Centre for Disease Prevention and Control (ECDC) risk assessment, which is updated regularly[5]. As further epidemiological data become available, the population groups considered vulnerable and at risk of severe infections could change.

The above-mentioned groups differ somewhat from the groups for whom many countries recommend seasonal influenza immunisation. Notably, elderly people are missing. It is speculated that elderly people are affected less because they possibly have some residual immunity from previous exposure to viruses in some ways similar to the pandemic (H1N1) 2009 influenza virus. However, it seems that not all elderly people are immune and those who do become infected suffer a more severe disease. Therefore some elderly people are at higher risk of developing severe disease, but they cannot be readily identified. Given this uncertainty, there is merit in including this age group as a target for vaccination.

1.3. Limiting the spread of infection: projection on immunisation coverage needed

To reduce or eliminate influenza from the host population, a reduction in transmission is necessary. This can be achieved by means such as vaccination. Vaccination is, epidemiologically speaking, an attempt to reduce the reproductive number R_0 (the number of secondary cases produced by each infectious case) to below 1.

The decisive question is what fraction of the population needs to be vaccinated in order to produce enough immune people to make sure that the infectious persons will not be able to infect one other person on average. If the fraction of the population susceptible is small

[5] http://www.ecdc.europa.eu/en/Health%5Ftopics/novel%5Finfluenza%5Fvirus/2009%5FOutbreak/.

enough, the probability that an infective host will come into contact with a susceptible individual before recovering will be very low.

For the current influenza pandemic, the estimates point to an R_0 value of about 1.6. Assuming a hypothetical vaccine efficacy of 70% (as often seen with seasonal influenza vaccines), the fraction of the population which would have to be vaccinated would be at least 54%[6].

This (over-)simplified calculation assumes that everybody would be equally affected by the disease, that there would be random mixing of the population, that the vaccine would have the same efficacy in everybody and that protective (susceptible) efficacy is equal to infectiousness efficacy. Nevertheless, it gives a rough indication to support policy decisions on immunisation coverage.

Epidemiological data on pandemic (H1N1) 2009 influenza suggest that immunisation of children and young adults could be particularly effective in reducing transmission.

2. POTENTIAL TARGET GROUPS AND PRIORITY GROUPS FOR VACCINATION

Target groups are all the people for whom vaccination can be recommended.

Priority groups are the people within the target groups who should be vaccinated first if not enough vaccine is initially available for everyone in the target groups. Even if enough vaccine were available, distributing large quantities of vaccine and vaccinating large numbers of people takes time.

Balancing the three objectives described previously, the following can be considered potential ***target groups*** for vaccination, covering between 34% and 60.5% of the total population:

- Maintaining essential services:
    - healthcare workers (2%);
    - workers in other essential services (4%).
- Protecting the vulnerable:
    - all persons aged from 6 months to 24 months (1.5%)[7];
    - all persons aged from 25 months to 64 years with underlying chronic conditions increasing the risk of severe disease (8%);
    - pregnant women (1.5%);

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[6] If a vaccine confers complete immunity on everyone who is immunised, a fraction $f > 1 — (1/R_0)$ would need to be vaccinated. If the vaccine confers immunity on only a fraction V1 of the population (not all vaccinated people will have a sufficient immune response to the vaccine to build up protective immunity), then f = V times V1 and thus $V > (1 — (1/R_0)) / V1$.

[7] The 0–6 months age group has not been included, given the absence of a vaccine for this age group. This vulnerable age group can be protected by other pharmaceutical and non-pharmaceutical public health measures. Immunising pregnant women will probably also afford some protection to newborns via maternal antibodies.

- all persons aged 65 years and more (17%)[8].

- Limiting the spread of infection, depending on the epidemiology, health service structures and available resources:

    - all persons aged from 25 months up to young adults, e.g. up to 18 years to cover children and young adults up to the end of secondary education (17%) or 24 years to cover children and young adults up to the end of tertiary education (26.5%).

It should be stressed that the eventual target groups will depend on the national targets set by the Member States. In some cases, this may be the entire population and in other cases only specific groups.

However, it is unlikely that the vaccine will be immediately available for all target groups at the same time and therefore, it is necessary to define priority groups. The European Union Health Security Committee and the Early Warning and Response authorities (HSC/EWRS) adopted on 25 August 2009 a policy statement[9] proposed by the European Commission in which the following 19.5% of the population was identified for ***prioritisation*** when limited amounts of vaccine are available:

- healthcare workers (2%);

- all persons aged from six months on with underlying chronic conditions increasing the risk of severe disease (16%);

- pregnant women (1.5%).

This prioritisation is designed to include the essential services which face the highest risk of being overloaded during a pandemic and also the vulnerable groups at greatest risk of severe illness following infection with the pandemic (H1N1) 2009 influenza virus.

It should be stressed that the responsibility for developing a vaccination strategy against pandemic (H1N1) 2009 lies with the Member States. Therefore, Member States may develop different vaccination strategies, taking into account their epidemiology, health service structures, available resources and cost-effectiveness of available vaccines.

The decisions on target groups and priority groups could also be influenced by the choice of pandemic (H1N1) 2009 influenza vaccine (e.g. adjuvanted versus unadjuvanted vaccine or inactivated whole virion vaccine versus surface antigen/split virus vaccine) and by marketing authorisation conditions for the available vaccines. and by the benefit/risk profile of available vaccines for individual population groups.

It should also be added that some of the above-mentioned groups might change as more epidemiological, clinical and pharmaceutical evidence becomes available and as the pandemic progresses. Potential target groups and priority groups for vaccination against pandemic (H1N1) 2009 influenza will therefore need to be reviewed regularly.

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[8] Given the uncertainty on whom has residual immunity from previous exposure to viruses in some ways similar to the pandemic (H1N1) 2009 influenza virus, there is merit in including this age group as a target for vaccination (see Section 1.2).

[9] http://ec.europa.eu/health/ph_threats/com/Influenza/docs/HSC_EWRS_statement_en.pdf

3. TIMING OF VACCINATION CAMPAIGNS

Vaccination of priority groups should start as soon as pandemic (H1N1) 2009 influenza vaccines become available. This should be followed by vaccination of target groups. It is recommendable to continue to vaccinate unimmunised individuals and not keep vaccine in reserve for later administration of the second dose. The second dose can be given three to four weeks later, as additional supplies become available.

4. VACCINATION CAPACITY OF HEALTHCARE SYSTEMS

4.1. Vaccine supply

First of all, vaccine supply will determine the vaccination capacity of healthcare systems. Prudent estimates put the annual global production capacity for pandemic influenza vaccine at 2.45 billion monovalent doses. European influenza vaccine manufacturers account for 60% of the global production capacity, i.e. approximately 1.5 billion monovalent doses, of which a large proportion could be exported outside Europe, as is the case for seasonal influenza vaccines. Also, the full annual production will only gradually become available. As a result, especially in the initial phase, demand could be higher than supply. Anticipating limited supplies, an increasing number of Member States have concluded advance purchase agreements with one or more influenza vaccine manufacturers to reserve a set proportion of the available production capacity for pandemic influenza vaccine.

4.2. Logistics

Appropriate arrangements will need to be made for distributing and storing sufficient quantities of vaccines and medical material (syringes, needles, alcohol swabs, etc.), including sufficient capacity to maintain the cold chain of vaccines. Administration of vaccines to target populations as soon as vaccine arrives should be the aim.

4.3. Vaccination capacity

To avoid overburdening healthcare facilities in the event of a mass vaccination campaign, Member States could consider spreading the settings in which vaccination will take place between healthcare facilities, schools, work places, function venues, etc., in accordance with any provisions in national and regional pandemic preparedness plans. In such cases, Member States would need to consider whether the chosen settings will be capable of providing vaccine, registering vaccination, recalling patients for their second dose within three or four weeks, depending on which vaccine is used, and monitoring and reporting adverse events.

Depending on the results of the scientific studies on the vaccine, either one or two doses of vaccine are expected to be needed to achieve protective immunity. Currently we are proceeding on the assumption of two doses; however should the scientific data indicate that one dose will be sufficient, more vaccines would become available to vaccinate in a shorter time those for whom vaccination can be recommended. In case two doses would be needed, it is recommendable to give the two doses of the same vaccine, as no clinical data are available on the interchangeability of different vaccines against pandemic (H1N1) 2009 influenza. Also, if doses of two different vaccines were given, it would be difficult to link adverse events, which do not manifest themselves shortly after immunisation, to a particular vaccine.

Member States will need to take into account in their budgets the financial and human resource implications of procuring and delivering the vaccine. As a planning assumption to ensure sufficient numbers of healthcare staff, a single vaccinator can vaccinate an estimated 50 to 100 individuals a day.

5. MONITORING AND EVALUATION OF VACCINATION CAMPAIGNS

5.1. Vaccine safety

The European Union has a comprehensive and effective monitoring system for reporting on and assessing the safety and efficacy of each medicinal product after it has been authorised. In addition, the European Medicines Agency (EMEA) has published specific guidance on the pharmacovigilance plan which forms part of the risk management plan that has to be submitted with the application for marketing authorisation for any pandemic influenza vaccine[10].

It is possible that when Member States launch a vaccination campaign against pandemic (H1N1) 2009, only limited safety data will be available. Therefore, Member States could consider establishing additional enhanced active surveillance for serious adverse events. Options could include using sentinel hospitals to screen actively for adverse events following immunisation or asking vaccinating doctors or nurses to report to the national authority on a weekly basis, irrespective whether they have seen any adverse event or not. Establishing protocols for assessing individual suspected cases of adverse events following immunisation, in order to ensure best practice, and determining background incidence rates of conditions on the list of adverse events of special interest before embarking on vaccination campaigns could be other key tools.

The activities described above will be essential in order to monitor closely any unexpected serious adverse reactions and allow the risk/benefit to be reassessed scientifically if necessary. If a vaccine shows serious side-effects, the Commission may — after a scientific assessment — vary, suspend or revoke its marketing authorisation.

Public confidence, and therefore the success of any vaccination campaign against pandemic (H1N1) 2009, will depend on the pharmacovigilance system in the EU working properly.

5.2. Vaccine effectiveness

Assessing and monitoring the effectiveness of pandemic vaccines is essential after vaccines are placed on the market and distributed for administration. Although strain-specific pandemic vaccines are expected to be effective against pandemic (H1N1) 2009 influenza, early availability of estimates of their effectiveness will allow better benefit/risk analysis if adverse events are reported following immunisation. Similarly, it will also allow better management of and response to reports of vaccine failures, i.e. of people contracting pandemic (H1N1) 2009 influenza despite having been vaccinated.

The effectiveness of the pandemic influenza vaccine will be studied by the vaccine manufacturers in collaboration with regulatory authorities. Effectiveness studies proposed after authorisation will be described in the risk management plan which has to be submitted

[10] http://www.emea.europa.eu/pdfs/human/pandemicinfluenza/35938109en.pdf.

with the application for marketing authorisation. Activities to monitor effectiveness could include specific effectiveness studies, prospective observational safety studies including effectiveness outcomes and the use of other sources of data such as local networks or sentinel physicians.

The ECDC is working with its partners (Epiconcept and Member States in the I-MOVE partnership[11]) to extend the mechanism it has developed for seasonal influenza to pandemic vaccines. It also maintains close links with its international partners planning to monitor the effectiveness of vaccines against pandemic (H1N1) 2009 influenza.

Should vaccine effectiveness be found to be poor, additional or alternative public health measures could be taken (e.g. antivirals) and further investigations could be conducted to improve vaccine use or composition.

[11] More information can be found at: http://ecdc.europa.eu/en/publications/Publications/0907_TED_Influenza_AH1N1_Measuring_Influenza_Vaccine_Effectiveness_Protocol_Case_Control_Studies.pdf.