ECDC HEALTH INFORMATION

Q&A for health professionals on vaccines and vaccination in relation to the 2009 influenza A(H1N1) pandemic

18 December 2009

Vaccines against 2009 pandemic influenza A(H1N1)

Q1. Which pandemic vaccines have been approved in Europe?

In the European Union, the European Commission has granted authorisation for three specific pandemic vaccines following a positive scientific opinion issued by the Committee for Medicinal Products for Human Use (CHMP) at the European Medicines Agency.

The products centrally authorised are Focetria® (Novartis), Pandemrix (GlaxoSmithKline) and Celvapan (Baxter). These vaccines are authorised for use in all Member States of the EU and the EEA (Iceland, Liechtenstein and Norway).

Several additional products have received a national authorisation in one or more European countries. As of 10 December these are known to include the following: The National Regulatory Agency in Hungary has provided a national licence to a pandemic vaccine, Fluval P, produced by the Hungarian manufacturer Omninvest. The National Regulatory Agency in France has provided a national licence for a pandemic vaccine, Panenza available in both single and multiple doses, produced by the manufacturer Sanofi Pasteur after filing a decentralised marketing authorisation application in six European Union countries. Authorisation in Belgium, Germany, Italy, Luxembourg and Spain will follow the authorisation in France (acting as the 'Reference Member State'). The German National Regulatory Agency has provided a national licence for a pandemic vaccine, PanVaxH1N1, produced by CSL in Australia. The Romanian National Regulatory Agency has provided a national licence for a pandemic vaccine, CANTGRIP, produced by Cantacuzino in Romania. Finally, the Swiss and German National Regulatory Agencies have provided national licences for a pandemic vaccine, Celtura, produced by the manufacturer Novartis.

Further pandemic vaccines from European manufacturers that regularly produce seasonal influenza vaccine may be developed and authorised within the coming months.

Q2. What do the pandemic vaccines contain?

All pandemic vaccines are based on an initial isolate of the new pandemic virus, specifically a strain called A/California/7/2009 (H1N1)v. The individual vaccine manufacturers have adapted the manufacturing process they

Prepared in conjunction with the European Medicines Agency and the European Commission. For more information see their respective websites on the pandemic: http://www.ema.europa.eu/influenza/home.htm and http://ec.europa.eu/health/communicable_diseases/diseases/influenza/h1n1/index_en.htm

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use for the seasonal and avian influenza vaccines. Hence the composition of the authorised European pandemic vaccines differ in conditions for virus propagation, antigen preparation, antigen content and whether they are adjuvanted or not (Table 1). All licensed vaccines in the European Union are inactivated and are administered intramuscularly. Four of the vaccines contain immunostimulating substances known as adjuvants and five contain the preservative thiomersal. For further details, see Tables 1 and 2.

Table 1: Overview of vaccines against 2009 pandemic influenza A(H1N1) available in the European Union in December 2009([a])

Name, producer([a])	Product description	Culture medium	Haemagglutinin content	Adjuvant emulsion	Number of doses
Celvapan, Baxter	Whole virion, wild-type A/California/7/2009 (H1N1)v, inactivated	Vero cell-derived	7.5 µg	None	All > 6 months([b]) 2 x 0.5 mL
Pandemrix, GSK	Split-virion, reassortant A/California/7/2009 (H1N1)v-like strain, inactivated, adjuvanted	Egg-derived	3.75 µg (per full dose)	AS03	Adults, adolescents and children ≥ 10 years([c]) 1 x 0.5 mL
			1.87 µg (per half dose([d]))		Children 6 months – 9 years 2 x 0.25 mL
Focetria, Novartis	Surface-antigens (haemagglutinin and neuraminidase), reassortant, A/California/7/2009 (H1N1)v-like strain, inactivated, adjuvanted	Egg-derived	7.5 µg	MF59C.1	Adults, adolescents and children ≥ 9 years([c]) 1 x 0.5 mL
					Children 6 months – 8 years 2 x 0.5 mL
Fluval P, Omnivest	Whole virion, reassortant A/California/7/2009 (H1N1)v-like strain, inactivated, adjuvanted	Egg-derived	6 µg (per full dose)	Aluminium phosphate	Adults and adolescents > 12 years 1 x 0.5 mL
			3 µg (per half dose([d]))		Children 12 months –12 years 1 x 0.25 mL
Panenza, Sanofi Pasteur	Split-virion, reassortant A/California/7/2009 (H1N1)v-like strain, inactivated	Egg-derived	15 µg (per full dose)	None	Adults, adolescents and children > 8 years 1 x 0.5 mL
					Elderly > 60 years and children 3 – 8 years 2 x 0.5 mL
			7.5 µg (per half dose([d]))		Children 6 – 35 months 2 x 0.25 mL
Celtura, Novartis	Surface-antigens (haemagglutinin and neuraminidase), reassortant, A/California/7/2009 (H1N1)v-like strain, inactivated, adjuvanted	MDCK cell-derived	3.75 µg	MF59C.1	Adults 18 – 40 years, children 3 – 17 years 1 x 0.25 mL
					Adults > 40 years 2 x 0.25 mL
PanvaxH1N1, CSL	Split-virion, reassortant A/California/7/2009 (H1N1)v-like strain, inactivated	Egg-derived	15 ug	None	Adults, adolescents and children > 9 years 1 x 0.5 mL
CANTGRIP, Cantacuzino	Split-virion, reassortant A/California/7/2009 (H1N1)v-like strain, inactivated	Egg-derived	15 ug	None	Adults ≥ 18 years 1 x 0.5 mL

(a) See Q1 for where vaccines are licensed.

(b) Immunogenicity data on Celvapan are still being assessed; evaluation may influence number of doses needed.

(c) For certain groups, such as younger children and immunocompromised patients, the recommendation for most of the authorised vaccines, unless otherwise stated in the Summary of Product Characteristics, is that two doses should be given, to ensure that their immune system responds adequately to the vaccination.

(d) Half dose recommended for use in children. Please note that the definition of 'children' varies among pandemic vaccines.

Q3. What are adjuvants and why are they used in some pandemic vaccines?

Some pandemic vaccines contain substances that enhance the immune response, so called 'adjuvants', which are substances that help boost the vaccine's potency[1]. As a result, a smaller amount of virus antigen is needed per person and, therefore, the current vaccine production will supply vaccines to many more people. Due to potential limitations of worldwide vaccine supply in the event of a pandemic and the propensity of influenza viruses to antigenic drift, the World Health Organization several years ago encouraged the development of vaccines with adjuvants when avian influenza vaccines were developed. As a result of adding adjuvants to pandemic vaccines, the production capacity of some manufacturers has increased by 100–200%, compared with their production of seasonal influenza vaccine. In spite of this increase there is not enough capacity to supply pandemic vaccine worldwide.

Two types of adjuvants are included in the pandemic vaccines: alum-based and squalene-based. Alum-based adjuvants, used by Omninvest, have been used in many different vaccines for the past 60 years and, therefore, the clinical experience is vast. Squalene-based adjuvants, used by Novartis and GSK, have been introduced more recently, but they have been used in seasonal influenza vaccines provided to older people since 1997. It is estimated that more than 45 million doses of squalene-containing seasonal influenza vaccine have been distributed in Europe.

Squalene is a natural substance found in plants, animals, and humans. It is an intermediate product of the endogenous human cholesterol metabolism and a component of human cell membranes. It is manufactured in the liver of humans and circulates in human blood. About 60–80% of ingested squalenes in food products are absorbed from the intestinal tract. Squalene is commercially extracted from fish oil; that used in pharmaceutical products and vaccines is purified from shark liver oil. It is also found in a variety of cosmetics, over-the-counter medications, and health supplements. For further information see Table 2.

One of the vaccine manufacturers (GSK) has added an additional immunostimulating compound, α-tocopherol (vitamin E) to their pandemic vaccine. α-tocopherol is a nutrient and the amount contained in the vaccine is within the recommended daily allowance for humans. For further information, see Table 2.

Table 2: Overview of thiomersal and immunostimulating substances included in vaccines against 2009 pandemic influenza A(H1N1) available in the European Union in December 2009

Name, producer	Thiomersal	Adjuvant emulsion
Celvapan, Baxter	None	None
Pandemrix, GSK	5 µg (per full dose) 2.5 µg (per halfdose(b))	**AS03** squalene(a) 10.69 mg α-tocopherol(a) 11.86 mg polysorbate 80 4.86 mg per full dose;
Focetria, Novartis	50 µg (in multidose vials)	**MF59C.1** squalene(a) 9.75 mg polysorbate 80 1.175 mg sorbitan trioleate 1.175 mg
Fluval P, Omninvest(c)	50 µg (per full dose) 25 µg (per halfdose(b))	aluminium phosphate(a) 0.33 mg Al3+ (per full dose) 0.165 mg Al3+ (per half dose(b))
Panenza, Sanofi Pasteur	45 µg (per full dose in multidose vials) 22.5 µg (per halfdose(b) in multidose vials)	None
Celtura, Novartis(c)	No	**MF59C.1** squalene(a) 4.875 mg polysorbat 80 0.588 mg sorbitanoleat 0.588 mg
PanvaxH1N1(c)	50 µg (in multidose vials)	None
CANTGRIP, Cantacuzino(c)	None	None

(a) Immunostimulating substances.
(b) Half dose recommended for use in children. Please note that definition of 'children' varies among pandemic vaccines.
(c) Provided in single dose vials, availability of multidose or single-dose vials may change over time.

[1] Atmar RL, Keitel WA. Adjuvants for pandemic influenza vaccines. Curr Top Microbiol Immunol. 2009;333:323-44.

Q4. What is thiomersal and why is it used in pandemic influenza vaccines?

Thiomersal is an antimicrobial organic mercury compound that is used either in the early stages of manufacturing, or as a preservative in the final product. It prevents influenza vaccines from becoming contaminated with microorganisms which can cause infection in vaccinated individuals. Pandemic influenza vaccines may include 2.5-50 µg thiomersal per dose as a preservative. Thiomersal contains 49.6% mercury (which amounts to 1.25–25 µg mercury per dose) and is metabolised into ethylmercury and thiosalicylate. See Table 2.

Q5. Is thiomersal safe when used as a preservative in vaccines?

Mercury is commonly found in foods, notably in fish and seafood, principally in the form of methylmercury. While exposure to methylmercury varies by country, intake estimates for European consumers are close to the internationally established safe intake limits. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has established a Provisional Tolerable Weekly Intake (PTWI) of methylmercury to 1.6 µg/kg body weight, equivalent to 96 µg in a 60-kg female. Acknowledging that there are different chemical forms of mercury (elemental, inorganic and organic), the conclusion is that, in view of the recommendations for food products, the total dose of thiomersal provided in one or two doses of pandemic vaccine is regarded to be of little significance and harmless to those vaccinated, which is also the experience from many years of its use in other vaccines[2].

Approximately 1–5% of adolescents and adults in Europe are considered to be allergic to thiomersal, having the potential to develop skin reactions. However, these reactions occur very rarely, and an existing thiomersal contact allergy is not a contraindication to the use of a thiomersal-containing vaccine. There have been case reports in the literature of occurrences of generalised allergic skin reactions to thiomersal after vaccination. However, over 90% of patients who have a contact allergy to thiomersal do not have an allergic reaction after intramuscular vaccination with thiomersal-containing vaccine.

Based on scientific data, WHO, the United States Institutes of Medicine and the European Medicines Agency have concluded that the evidence favours the rejection of a causal relationship between thiomersal-containing vaccines and autism[2].

Q6. How many doses of vaccine are required for an initial robust immune response?

The current recommendation from the European Medicines Agency, after reviewing the immunogenicity data from the first clinical trials with two of the centrally authorised vaccines (Focetria and Pandemrix) is of two doses at least three weeks apart for young children and the immunocompromised, while all other groups are recommended a single dose (see Table 1). With more data on immunogenicity becoming available, recommendations may also change for younger children. Data on the latest centrally authorised vaccine (Celvapan) are still being assessed by the European Medicines Agency and therefore two doses at least three weeks apart are still recommended (see table 1). Some published studies report good immunological responses to a single dose three weeks after dose one, confirming that an initial robust immune response does evolve, but this needs to be followed to establish the long-term effect[3].

[2] Thompson WW, Price C, Goodson B, Shay DK, Benson P, Hinrichsen VL, et al. Early thimerosal exposure and neuropsychological outcomes at 7 to 10 years. N Engl J Med. 2007;357(13):1281-92.
Tozzi AE, Bisiacchi P, Tarantino V, De Mei B, D'Elia L, Chiarotti F, et al. Neuropsychological performance 10 years after immunization in infancy with thimerosal-containing vaccines. Pediatrics. 2009;123(2):475-82.
Aschner M, Ceccatelli S. Are neuropathological conditions relevant to ethylmercury exposure? Neurotox Res. 16 September 2009 [Epub ahead of print]. doi:10.1007/s12640-009-9113-2.
Burbacher TM, Shen DD, Liberato N, Grant KS, Cernichiari E, Clarkson T. Comparison of blood and brain mercury levels in infant monkeys exposed to methylmercury or vaccines containing thimerosal. Environ Health Perspect. 2005;113(8):1015-21.
Institute of Medicine of the National Academies. Immunization Safety Review: Vaccines and Autism. Washington, DC: The National Academies Press; 2004. Available from: http://books.nap.edu/openbook.php?record_id=10997

[3] Greenberg ME, Lai MH, Hartel GF, Wichems CH, Gittleson C, Bennet J, et al. Response after one dose of a monovalent influenza A(H1N1) 2009 vaccine – preliminary report. N Engl J Med. 10 September 2009 [Epub ahead of print]. doi:10.10656/NEJMoa0907413.
Clark TW, Pareek M, Hoschler K, Dillon H, Nicholson KG, Groth N, et al. Trial of influenza A(H1N1) 2009 monovalent MF59-adjuvanted vaccine – preliminary report. N Engl J Med. 10 September 2009 [Epub ahead of print]. doi:10.1056/NEJMoa0907650.

The full details of the European Medicines Agency's recommendations can be found in the Summary of Product Characteristics (SPC), which details how the vaccine may be used and describes the data on which its recommendations are based. The SPC for Focetria, Pandemrix and Celvapan can be found on the Agency's web page. Based on this information, governments in each EU Member State will develop their vaccination strategy.

In accordance with scientific evidence obtained in clinical trials with the avian influenza A(H5N1) vaccine, the Hungarian manufacturer Omnivest recommends one dose of its vaccine, Fluval P, to everyone over 12 months of age[4].

In addition, for the newly licensed pandemic vaccines Panenza, one dose is recommended to all age groups except children 3 – 8 years old and adults > 60 years old; for Celtura, one dose is recommended for individuals aged 3 – 40 years, while individuals > 40 years old are recommended two doses; for PanvaxH1N1 one dose is recommended to all > 9 years old; for CANTGRIP one dose is recommended to everyone > 18 years old. See Table 1.

Q7. Will booster doses be needed long-term?

The long-term immune response to these vaccines must be followed in clinical trials and, if waning immunity is observed, a booster dose may be warranted and recommended accordingly by the European Medicines Agency. Seasonal influenza vaccine recommendations are updated annually. It is not known today if the current pandemic influenza strain will be included in future seasonal influenza vaccines or will remain separate.

Q8. Will we need to be vaccinated every year against pandemic influenza?

A large number of Europeans had not previously experienced infections with this type of influenza virus, they are so called naive to the new strain. The current strategy with the pandemic vaccines is mainly aimed at priming (i.e. initiating an immune response) naive subjects and rapidly achieving protective immunity. However, it is known from clinical trials with avian influenza vaccines (against A(H5N1)) and other seasonal influenza vaccines that antibody titres tend to wane over time and booster doses may therefore be needed. Data from on-going trials will guide decisions on whether they are necessary. Moreover, virus mutations are likely to occur over time and may necessitate updated vaccines.

Both adjuvanted and unadjuvanted pandemic vaccines have been shown to provide a good immune response. Adjuvanted vaccines commonly provide a stronger immune response than unadjuvanted vaccines and also provide a broader immune response allowing for some potential drift of the influenza virus.

Effectiveness of the current vaccines in Europe is being assessed in large epidemiological studies. Breakthrough infections occurring in spite of vaccination, indicating a poor match between the given vaccine and circulating strains, will be reported as an adverse event and will be one of the tools to assess effectiveness.

The possibility of including the pandemic strain in future seasonal influenza vaccinations is being evaluated.

Q9. How safe are the pandemic vaccines?

Based on information received from 16 countries, WHO estimates that around 80 million doses of pandemic vaccine have been distributed and around 65 million people have been vaccinated[5]. National immunisation campaigns began in Australia and China in late September and in several European countries during the month of October. More than 25 million individuals have been vaccinated in the European Union.

Globally vaccination campaigns are using unadjuvanted inactivated vaccines, adjuvanted inactivated vaccines, and live attenuated vaccines (this last group is not licensed in Europe). Although intense monitoring of vaccine safety continues, all data compiled to date indicate that pandemic vaccines match the excellent safety profile of seasonal influenza vaccines, which have been used for more than 60 years.

[4] Johansen K, Nicoll A, Ciancio BC, Kramarz P. Pandemic influenza A(H1N1) 2009 vaccines in the European Union. Euro Surveill. 2009;14(41):pii=19361. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19361

[5] WHO. Pandemic (H1N1) 2009 briefing note 16: safety of pandemic vaccines: Geneva: 19 November 2009. Available at: http://www.who.int/csr/disease/swineflu/notes/briefing_20091119/en/index.html

Q10. What are the expected side effects of the pandemic vaccines?

The adverse events so far reported have been mainly mild and transient symptoms. As anticipated, side effects commonly reported include swelling, redness or pain at the injection site, which usually resolves spontaneously a short time after vaccination. Fever, headache, fatigue, and muscle aches, occurring shortly after vaccine administration, have also been reported, though with less frequency. These symptoms also resolve spontaneously, usually within 48 hours. In addition, a variety of allergic reactions including urticaria and anaphylaxis have been observed. The frequency of these reactions is within the expected range. A very small number of cases of Guillain-Barré syndrome and fetal death have been reported. The number of cases is in line with normal background rates on a population basis, as reported in a recent study[6]. The European Medicines Agency is still in the process of gathering all relevant information and evaluating the reports but on the basis of the available information the Agency states that no link to the vaccines has been established.

Several European National Regulatory Agencies as well as the European Medicines Agency are regularly publishing reports on their adverse event monitoring. The WHO Uppsala Monitoring Centre has compiled a list of all Agencies worldwide that report adverse events following immunisation. Several Agencies specifically report adverse events among pregnant women and children but none is specifically reporting on chronically ill or immunocompromised individuals with any of the pandemic vaccines as yet. This is commonly the case with vaccines and must be addressed in specifically designed trials and registry studies.

As with any medicinal product, serious adverse events may occur. There are a very few individuals – those who have a severe allergy (life-threatening) to chicken, egg or any other substance in the more common egg-based vaccines – for whom vaccination with those vaccines is not recommended. However, there are now several alternative vaccines for egg-allergic individuals available, though not necessarily in all Member States. Cell-based pandemic vaccines have been licensed in some European countries and are likely to become more readily available. In addition, the results from a first rapid clinical trial[7] by the Canadian influenza research network, sponsored by the Public Health Agency of Canada, providing an egg-derived adjuvanted pandemic vaccine to more than 900 patients with documented egg allergy were released as a news item in the Canadian Medical Association Journal. After vaccinating 952 children and adults, two mild allergic cutaneous reactions were treated and no severe reactions developed. As a result of this trial the Canadian researchers are now recommending a change in the guidelines for vaccinating egg-allergic patients so that allergists need not be present, as long as a physician is close by and the vaccine is administered in a hospital setting. They suggest that patients judged to have a more severe risk of anaphylaxis should first receive 10% of the usual dose and the remaining 90% roughly 10 minutes later, provided they have not had a reaction to the first dose. Patients who receive the full dose directly should stay in the waiting room for 60 minutes instead of the recommended 15 minutes.

Q11. How is safety monitored?

The routine pharmacovigilance system within EU Member States will continue and reports of serious and unexpected adverse reactions will be sent as usual for the centrally authorised vaccines, to the European Medicines Agency's EudraVigilance database. These results are published weekly. Manufacturers are requested to send simplified periodic safety update reports (PSURs) on a monthly basis to the Agency. In addition, manufacturers have been requested to carry out a post-authorisation observational safety cohort study in 9 000 subjects for each vaccine and to establish the mechanisms to promptly investigate issues affecting the benefit-risk balance of their vaccine. Several European National Regulatory Agencies as well as the European Medicines Agency are regularly publishing reports from their adverse event monitoring. In addition, ECDC, in collaboration with a consortium of researchers, is developing complementary vaccine safety monitoring through linkage of large computerised clinical databases and immunisation registries.

For nationally authorised pandemic vaccines, monitoring and reporting will be conducted in the respective countries.

6 Black S, Eskola J, Siegrist C, Halsey N, MacDonald N, Barbara Law, et al. Importance of background rates of disease in assessment of vaccine safety during mass immunisation with pandemic H1N1 influenza vaccines. Lancet. 2009 Oct 30. [Epub ahead of print]. doi:10.1016/S0140-6736(09)61877-8.

[7] Canadian Medical Association. Egg-allergic patients gain greater access to pandemic vaccine [News]. doi:10.1503/cmaj.109-3123. Available at http://www.cmaj.ca/earlyreleases/2dec09-egg-allergic-patients.shtml.

Q12. Will the seasonal influenza vaccine also protect against the pandemic influenza A(H1N1) virus?

The seasonal influenza vaccine has not been shown to protect against pandemic influenza (H1N1) 2009 because the viruses are quite dissimilar despite having the same nomenclature.

Q13. Is seasonal influenza vaccination still necessary for someone who has been vaccinated against pandemic influenza (H1N1)?

Individuals recommended to receive the seasonal influenza vaccine regularly, according to national recommendations, should also this year receive the seasonal influenza vaccine. The experience from the winter season in the southern hemisphere suggests that influenza A(H3N2) and influenza B circulated concomitantly with the pandemic influenza A(H1N1) virus in varying degrees. Without immunising, older people and individuals with chronic conditions, in particular, would be left very vulnerable if seasonal influenza strains will continue to circulate even in small amounts.

Q14. Can the seasonal vaccine and the pandemic vaccine be given at the same time?

Clinical trials evaluating the impact on the immune response of seasonal influenza vaccines by adjuvanted pandemic influenza vaccines have been performed. Data were recently assessed by the European Medicines Agency and it was concluded that the adjuvanted vaccines Focetria and Pandemrix can be co-administered with non-adjuvanted seasonal influenza vaccines[8]. For the other licensed pandemic vaccines the generally accepted rule of providing inactivated influenza (H1N1) vaccine at the same visit as any other inactivated vaccine, including the pneumococcal polysaccharide vaccine may be followed. However, it is recommended to administer vaccines in different sites (e.g. one in each arm) as should there be a local reaction this identifies which vaccine that is to.

Q15. Should vaccination against pandemic influenza (H1N1) 2009 be given to a person who has had influenza-like illness since the spring of 2009?

Vaccination of a person with some existing immunity to the pandemic virus will not be harmful. The symptoms of influenza are similar to those caused by many other viruses causing upper respiratory symptoms. Even at the peak of the influenza season, other viruses are also causing disease (e.g. respiratory syncytial virus, parainfluenza, adenoviruses, etc.). Since most people with influenza-like illnesses have not been tested for influenza A(H1N1)v, the majority will not know whether they have been infected with the new influenza virus or a different virus. Therefore, if a person was ill but does not know whether they had influenza (H1N1) 2009, they should be vaccinated.

8 European Medicines Agency. European Medicines Agency reaffirms efficacy and safety of H1N1 pandemic vaccines [press release]. London, 20 November 2009. Available at: http://www.emea.europa.eu/pdfs/human/press/pr/74870709en.pdf.

Vaccination against pandemic influenza (H1N1) 2009

Q16. Will vaccination have an impact on the pandemic influenza (H1N1) 2009?

To prevent or ameliorate a wave of transmission in a pandemic, a large proportion of the population would need to have acquired immunity either through vaccination or naturally. As the vaccine has only become available this autumn in Europe most countries have not been able to deliver the vaccine to sufficient numbers soon enough to prevent or even ameliorate the transmission waves The vaccination strategy therefore has been primarily the same as for seasonal influenza that of protecting the vulnerable. Nevertheless, providing vaccine to other groups will likely have decreased the impact of the pandemic. Offering vaccine to selected risk groups will provide them with individual protection. For individuals in risk groups that cannot receive the vaccine (children < 6 months old) or respond poorly to vaccines (individuals undergoing immunosuppressive treatment), it is important that household members and healthcare workers consider receiving the vaccine in order to provide optimal protection to the people in their care. In addition, they will be protected themselves.

Q17. When will vaccination start in the different EU Member States?

In the European Union, a total of eight pandemic vaccines have been granted either central authorisation by the European Commission or national authorisation. Therefore, the tools for starting vaccination campaigns are now available in many European Member States. However, the limited vaccine supply in the coming months, as well as different tempo of preparation, has resulted in some diversity, and vaccination campaigns have started at different times in different countries/regions depending on availability of vaccines and preparation.

Q18. Who should be vaccinated?

The decision on who will be offered vaccine is the responsibility of the Member States and individual doctors advising their patients.

Please see Q19 for a policy statement on target and priority groups recommended for vaccination, as adopted by the EU Health Security Committee and Early Warning and Response Scheme. The identified priority groups should serve as indication only and countries may wish to adapt – and some have already done so – the prioritisation in line with their epidemiology, health service provision and resources.

Q19. Who is being vaccinated first?

The responsibility and mandate for developing a vaccination strategy for influenza (H1N1) 2009 lie with each Member State, but the European Commission is coordinating efforts and ECDC has issued its guidance in both a longer document and a shorter health education format[9].

The EU Health Security Committee and the Early Warning and Response authorities adopted on 25 August 2009 a policy statement on target and priority groups for vaccination, recommending the following groups as constituting the first priority groups for (H1N1) 2009 vaccination, in no priority order between the categories:

- All adults and children older than six months with underlying chronic conditions (see Q21 for definition of underlying conditions).
- Pregnant women.
- Healthcare workers.

[9] http://www.ecdc.europa.eu/en/healthtopics/Documents/0908_Influenza_AH1N1_On_the_use_of_specific_pandemic_influenza_vaccines.pdf

Q20. Which are the risk groups for developing severe disease due to the pandemic virus?

A small proportion of those infected have been affected severely, including some cases of hospitalisations and deaths, despite adequate medical care. These more severe cases have been reported mostly among 'risk groups'. However, it should be noted that around 30% of deaths have occurred among individuals who did not have any underlying conditions[10].The 'risk groups' identified for pandemic influenza (H1N1) 2009 are very similar to the ones identified as being in the 'clinical risk groups' for seasonal influenza, published in Eurosurveillance, Volume 13, Issue 43, of 23 October 2008: but with the addition of pregnant women and young children

- Clinical risk groups: People of all ages with chronic underlying conditions – diabetes, cardiovascular disease, chronic respiratory disease, including moderate and severe asthma, and other conditions that impair breathing and cause other chronic health problems such as extreme obesity and some physical handicaps.
- Pregnant women.
- Young children (especially those under two years of age).

In children, the clinical risk groups are somewhat different, with more emphasis on neurodevelopmental handicaps and less on chronic medical conditions such as diabetes and cardiovascular disease.

Q21. Why are pregnant women a 'risk group'?

A pregnant woman who develops the pandemic influenza is four to five times more likely to become sufficiently ill to be hospitalised compared with other adults. Data from the United States suggest that risk of hospitalisation increased throughout pregnancy[11]. In addition, studies of critically ill patients in Australia and New Zealand suggest that almost 10% of patients admitted to intensive care are pregnant women – a tenfold increase on what would normally be expected. In several studies, a majority of the pregnant women were healthy prior to the influenza (H1N1) infection, with no underlying disease.

This is not a surprise as the same is true for seasonal influenza[12], but to a lesser extent. The risk from seasonal influenza increases as pregnancy advances and is highest in the second and third trimesters of the pregnancy. That is why some countries recommend giving pregnant women seasonal influenza vaccines which has been carried out for some time with no ill effects.

This is why ECDC and other authorities like WHO and the US CDC consider pregnant women as a 'risk group'. However, it is important not to overstate the risk to the individual. Most pregnant women are still much more likely just to have a mild self-limiting infection that will not require hospitalisation.

Q22. What are the advantages of immunising pregnant women?

The immunisation will not only protect the mother-to-be but it will also give direct and indirect protection to the newborn child not eligible for vaccination until the age of six months.

Q23. Are pandemic influenza vaccines safe for pregnant women and children?

It is estimated that more than 25 million Europeans, including pregnant women and children in different age groups, have been vaccinated so far [4 December 2009]. Most individuals have received the centrally authorised vaccines Pandemrix, Focetria and Celvapan. The adverse events reported so far have mainly been symptoms such

[10] For more detailed information, see the latest ECDC Risk assessment.

[11] Jain S, Kamimoto L, Bramley AM, Schmitz AM, Benoit SR, Louie J, et al; 2009 Pandemic Influenza A (H1N1) Virus Hospitalizations Investigation Team. Hospitalized patients with 2009 H1N1 influenza in the United States, April-June 2009. N Engl J Med. 2009 Nov 12;361(20):1935-44. Epub 2009 Oct 8.
Jamieson DJ, Honein MA, Rasmussen SA, Williams JL, Swerdlow DL, Biggerstaff MS, et al; Novel Influenza A (H1N1) Pregnancy Working Group. H1N1 2009 influenza virus infection during pregnancy in the USA. Lancet. 2009 Aug 8;374(9688):451-8. Epub 2009 Jul 28.

[12] Skowronski DM, De Serres G. Is routine influenza immunization warranted in early pregnancy? Vaccine. 2009 Jul 30;27(35):4754-70. Epub 2009 Apr 16.

as fever, nausea, headache, allergic reactions and injection site reactions, confirming the safety profile of the centrally authorised vaccines. New clinical trial data showed greater incidence of fever following the second dose of Pandemrix in infants aged 6 – 35 months. An assessment of these data is ongoing.

Several National Regulatory Agencies specifically report on events after immunisation of pregnant women and children[13].

Q24. What studies have been done on the influenza (H1N1) vaccines and have any been done in pregnant women?

Studies to test the influenza (H1N1) 2009 vaccines in healthy children, adults and the elderly are being done now by each European manufacturer for each vaccine. Immunogenicity and safety data from clinical trials are available from healthy adults for all the pandemic vaccines used in Europe and results from other groups will be reported as soon as available. From safety monitoring of > 200 000 pregnant women there are no reports of problems beyond those experienced by other vaccinated individuals. Examples of research activities and monitoring following vaccination with pregnant women are available from the European Strategy for influenza A/H1N1 vaccine benefit risk monitoring.

Q25. Can the pandemic vaccine be given at any time during pregnancy?

Most European countries recommend that all pregnant women be vaccinated. From safety monitoring of > 200 000 pregnant women receiving adjuvanted and unadjuvanted vaccines, there are no reports of problems beyond those experienced by other vaccinated individuals. Increased severity of H1N1 infections has been reported with increased gestational age.

Q26. Can a breastfeeding mother receive pandemic influenza vaccine?

Both seasonal influenza and pandemic influenza (H1N1) vaccines can be given to breastfeeding mothers. Breastfeeding is fully compatible with flu vaccination, and preventing the flu in mothers will reduce the chance that the infant will get influenza. This is especially important as children under six months currently cannot be immunised against influenza due to a lack of clinical trials in this age group.

Also, by breastfeeding, a mother can pass on to her baby the antibodies that her body makes in response to the pandemic influenza vaccination, which can reduce the baby's chances of getting sick with influenza.

Q27. Are adjuvanted vaccines safe for pregnant women?

From safety monitoring of > 200 000 European women, who received mainly adjuvanted pandemic vaccines, there are no reports of problems beyond those from other vaccinated individuals. In addition, > 50 000 pregnant Canadian women have received the adjuvanted vaccines, similarly without any problems reported beyond those in other groups. Adjuvanted vaccines are associated with a higher rate of local reactions and mild flu-like symptoms. As mentioned earlier, the adjuvanted vaccines have a number of advantages in that they probably give longer lasting and broader protection than non-adjuvanted vaccines.

Q28. Is thiomersal safe for a pregnant woman and her unborn child?

There is no evidence that thiomersal (a mercury preservative in vaccine that comes in multidose vials) is harmful to a pregnant woman or a fetus. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has established a Provisional Tolerable Weekly Intake (PTWI) of 1.6 µg methylmercury/kg body weight specifically for pregnant women, equivalent to 96 µg in a 60 kg female. In view of the recommendations for food products, the total dose of thiomersal provided in one or two doses of pandemic vaccine is regarded as of little significance and harmless to those vaccinated, which is also the experience from many years of its use in other vaccines.

[13] See the Swedish National Regulatory Agency and the UK Medicines and Health care products Regulatory Agency.

Q29. Why are people aged 65 and over not considered to be in the risk groups for the pandemic influenza (H1N1), given that this is the case for seasonal influenza?

In a large case-series study of a total of 272 hospitalised patients from the US, only 5% of the patients were 65 years of age or older[14]. It is most likely that this age group has some residual immunity and, in fact, in some individuals older than 65 years living in the US reactive antibodies to the new (H1N1) 2009 virus have been shown[15]. This is suggestive of previous exposure to a similar virus. However, people in the clinical risk groups of any age (apart from children under six months old) are recommended to have these vaccinations.

Q30. Why is the pneumococcal polysaccharide vaccine recommended for certain risk groups and people 65 and over?

Pneumococcal secondary infections complicating the influenza (H1N1) infection have been shown in smaller case-series studies[16]. That is the reason why individuals older than 65 years and other risk groups that are regularly recommended to receive pneumococcal polysaccharide vaccines should be vaccinated following national recommendations.

More information about pandemic influenza (H1N1) 2009 can be found at the ECDC website: www.ecdc.europa.eu

[14] WHO. Pandemic (H1N1) 2009 briefing note 13: Clinical features of severe cases of pandemic influenza. Available at: http://www.who.int/csr/disease/swineflu/notes/h1n1_clinical_features_20091016/en/index.html.

[15] CDC. Serum cross-reactive antibody response to a novel influenza A (H1N1) virus after vaccination with seasonal influenza vaccine. MMWR Morb Mortal Wkly Rep. 2009 May 22;58(19):521-4.

[16] CDC. Bacterial coinfections in lung tissue specimens from fatal cases of 2009 pandemic influenza A (H1N1) - United States, May-August 2009. MMWR Morb Mortal Wkly Rep. 2009 Oct 2;58(38):1071-4.