



Transcript of WHO Virtual Press Conference of 6 August 2009 with Dr Marie-Paule Kieny, Director of the Initiative for Vaccine Research at WHO Headquarters and Gregory Hartl, Spokesperson for H1N1

HARTL: Good afternoon. This is the World Health Organization in Geneva. Welcome to our virtual press briefing for today 6 August 2009.

With us today is Dr Marie-Paule Kieny, Director of the Initiative for Vaccine Research here at WHO headquarters who will brief you on developments regarding vaccine development for pandemic H1N1 virus. So just to let you know that after the VPC is over we will post as soon as possible thereafter an audio file and a transcript. For those of you who would like to ask questions, please dial 0 1 to enter the queue.

Thank you very much and welcome and I hand over to Dr. Marie-Paul Kieny.

KIENY: Thank you very much. So in my update on vaccines, I will cover three points.

One is the state of development of the vaccines. Second, I will try to address concerns that have come into the press about safety, and finally I will also talk about future availability and how we see at this point as of today when this vaccine will be available first for use.

So about status of development first. As you know the vaccine viruses, which are really the starting material that the manufacturers need to produce vaccine, have been provided to all manufacturers. There have been more than 400 shipments of viruses and reagents to the manufacturers. So all this has been now mastered by quite a number of weeks by the WHO Collaborative Centres.

In terms of real production, the manufacturers have adapted these vaccine viruses to grow in their particular conditions, and they have produced lots of batches if you wish. So these are the material, it's concentrated, it's an experimental vaccine that can be now used for clinical trials and some of the batches, the larger batches, are also the ones that will be used for real application and implementation of vaccination campaigns.

So the data and all the controls on these vaccine lots are being submitted right now to regulatory agencies, in order to allow these regulatory agencies to look at the data presented by the manufacturers, and to take decision on their safety and suitability for use in the population.

In terms of clinical trials, we have now seven manufacturers who have started clinical trials and these clinical trials as I speak are going on in at least five countries. These countries are China, Australia, the United Kingdom, Germany and the U.S.A. We expect that more clinical trials will start in the days to come, really this is something which is



happening as we speak today and these clinical trials will of course be conducted in additional countries to the list that I just gave.

So when do we expect to have results of the first clinical trials and what will the clinical trial results tell us?

So for the clinical trials that have started in July already, we should have early results during the first half of September.

What will these trials tell us?

They will tell us whether we will need one or two doses per person for vaccination. You certainly know that for seasonal vaccination it is only one dose that is required. For H5 Avian virus, however, there was a need to have two doses of vaccine per person to induce the level of protection that would be required against an infection. So we will know after these clinical trials whether one or two doses are needed and this will also give confirmation that the formulation that the manufacturers are using are indeed immunogenic and are likely to induce protection against the pandemic virus.

So really in conclusion in terms of development we are on track in development. We have put on our website in Vaccine Question and Answers, that it takes between five and six months to develop a new influenza vaccine for a pandemic application. As you will calculate we are absolutely on track with that and WHO will post as of today a new document on our website which will really detail the different steps which are needed to make a pandemic influenza vaccine, and details also on the length of the steps and description of how it takes five to six months.

The next point that I would like to cover is on safety.

So there have been concerns voiced in the press but mainly the time lines for the development of these vaccines is so quick that it would not assure safety. So I would like to make clear that for all vaccines have a safety profile. There is no vaccine that induces zero safety concerns. Most of the safety concerns induced by the vaccine which are apart from that, very, very safe medicines, as (unintelligible) some fever sometimes, potentially nausea, so very minor side effects, but in a very rare occurrence from many vaccines, there can be the occurrence of a more severe adverse event. So there is no doubt that if and when there will be very large scale vaccination campaign, there will be people who will have an adverse event. The large majority of these events will not be associated at all with the vaccine which is given. It will be temporally associated which means this is something that would have happened anyway, but which just by chance is happening after a person has had a vaccination.



So the regulatory authorities in all countries will monitor very closely all sickness as adverse events, and will try immediately to decipher whether indeed these side effects are linked to the vaccine, or whether they are just coincidental.

In terms of assuring most specifically the safety of influenza vaccines, I would like also to point out that part of the vaccines are based on very old and proven technology which are used for seasonal vaccination.

So for seasonal vaccines, million upon millions of doses have been administered to all kinds of populations, including very young children, and including pregnant women. For those vaccines where the technology remains exactly the same as for seasonal vaccines, what happens or the way it is treated, is called a "strain change". So this is no different to making a vaccine for the seasonal flu in 2006 and making the change to making the 2007 vaccine. So regulatory agencies in the world have different ways of treating these so-called strain changes.

In the USA for example, the FDA approves a strain change by looking at the quality control dossier that the manufacturer submits and does not require a clinical trial. Therefore, for those pandemic vaccines that will be like a strain change, only it will be H1N1 instead of another seasonal strain, the FDA has decided that they will treat this as a normal strain change and, therefore, the vaccine will be registered without clinical trials.

All manufacturers of course will conduct a clinical trial if only to confirm whether one or two doses are needed as I said a few minutes ago.

In Europe the procedure for registration of seasonal influenza vaccine is slightly different. In the sense that the regulatory authority requests every year a small clinical trial of the new seasonal vaccine. Therefore, in Europe, for those vaccines that are made using the exact same procedure, they are copies if you wish of seasonal vaccines, the European regulatory agency will review the dossier, will request a small clinical trial, and will register after that exactly like for seasonal vaccines.

Now for pandemic use, there are a number of vaccines which are not the classical seasonal vaccines. These are the vaccines which have an addition of an adjuvant. These adjuvanted vaccines have been tested extensively at the time when all manufacturers were preparing vaccines for a potential H5N1 pandemic. In view of the potential gravity of an H5N1 vaccine, the European Regulatory Agency had designed a special process by which manufacturers would test extensively in clinical trials, prototypes of H5N1 vaccines, including with adjuvants, which submit all the safety data of clinical trials, immunogenicity to the regulatory agency and obtain what is called a "mock-up registration". So this is a registration for a prototype.

So those manufacturers who do have a mock-up dossier can go and present to the EMEA all their documentation for the H1N1 vaccine and as previously agreed already in 2007



with the regulatory authority, obtain registration without clinical trials. But again as I said for the USA, all manufacturers will conduct clinical trials and the earliest results of these clinical trials will be available in September.

Finally, about future availability. Well, as you know, it is one thing to have vaccine lots, even commercial lots ready in the fridge, and to be able to use it in the population. So the step which is required in between having the physical material ready, and using it in the population, is "licensing" by regulatory authorities. Now the manufacturers have started now to submit these dossiers to the regulators and to expect that the regulators will make decisions on these vaccines that will allow use in populations during September when the first authorization may be in September, and then going further into October, when the dossiers are ready and are submitted by the manufacturers.

So with this update I will be very happy to answer any questions that you might have.

HARTL: Dr Kieny, thank you very much for that very thorough update. Now before we go to questions can I please remind journalists that there will be an audio file available almost immediately after this briefing is over, and shortly later, there will be a transcript on the web site. For journalists who are wanting to ask a question, please dial zero one (01) to get into the queue.

The first question is from Jonathan Lynn of Reuters.

LYNN: Could you tell us something about the likely yields of the vaccines that are being developed at the moment on the basis of the trials.

KIENY: The early yields that the manufacturers have obtained with the vaccine viruses, with the seed that they have made out of vaccine viruses that have been provided by WHO Collaborative Centres, have been quite disappointing. Indeed we have had news and discussions with all of the manufacturers and they were reporting yields which were between a third and a half of what they usually get for a good seasonal strain.

So this is certainly of concern because this would mathematically result in a reduction by the same factor of a production capacity. So the WHO Collaborating Centres have been starting immediately to produce new vaccine viruses and we need to wait for a few days to have real confirmation but the latest result that we've heard as of this week is that at least one of the strains which has been produced, seems to have been promising and seems to give equivalent or similar yields as the ones that the manufacturers have for seasonal vaccine. So I don't want to say too early that the question (situation) has been resolved but it really seems we have found a way to go around this problem.

Mr GOLD, DPA: Hi, thank you very much for taking my question. I just wanted to ask one thing, when you mentioned the names of the countries that are doing research you didn't mention Switzerland. But Novartis announced that they have begun clinical trials.



Is that from the US arm, or is it not something WHO has been told about? And what is the possibility there are a lot more trials going on that maybe the WHO is not aware about?

Secondly, because the sound was rather bad, could I ask you to just repeat very briefly the European regulations and how the Europeans are going to be testing the new vaccines.

KIENY: So as to countries, Novartis to the best of our knowledge, has started the first trial in the UK and this was a vaccine they had produced using "cell culture" and not in eggs and since then they have also started clinical trials in Germany and in the US. So of course, as clinical trials start these days, right now, it may well be possible that another clinical trial is starting today that we don't know about. We do have communication and an excellent relationship with the regulators and the manufacturers and we have really frequent update of the latest development. So yes it may well be that another clinical trial has started somewhere else.

So going back to the registration of influenza vaccines in Europe.

What I said is that the normal registration procedure in Europe for seasonal vaccine includes a small clinical trial. And this is for a seasonal strain, which is therefore, a change from one year to another is considered as a "strain change." And in Europe, in addition to reviewing the dossier that the industry produces, the European Medicines Agency also request the results of a small clinical trial.

So for vaccines which are the same as seasonal vaccines, if you wish, using the same procedure, just in changing the strain, the European Medicine Agency will of course continue to request a clinical trial.

For those vaccines where the formulation that is proposed by the industry is different from that of the seasonal vaccines, which is based on the formulation, which has been discovered if you wish, or developed, for H5N1 pending future or potential future pandemic vaccines, for those manufacturers who have what is called a "mock-up registration" so this is a registration of a prototype pandemic vaccines, the agreement and the procedure that was reached already in 2007 was that in order to ensure as early as possible the availability of vaccines, that the manufacturers could submit their quality dossiers, so this is all the results on characterization of a protein, and also of course toxicity, all lots of vaccines are tested in animals for toxicity, so that if preclinical studies on all vaccines, and could submit this dossier and that they could be approved without clinical trials. This is a procedure which is nothing new and has not been invented for H1N1. This is something that has been put into place at a time when we were more worried by H5N1 than by the current pandemic.

MICHELE CORTES, BLOOMBERG: Yes, I'm wondering if you can tell us how many doses we are going to expect of the adjuvanted vaccine and the regular seasonal



strain, where you have the strain changed. And also in the US where they don't have any adjuvanted vaccine at all at this point, I'm wondering what the process will be there in terms of either using the strain change or adjuvanted vaccine.

KIENY: So let me address the second question first. The US regulators will approve vaccines which are based on the seasonal production process, as I said. For the others of course they will look at the adjuvanted vaccines but because these vaccines have never been licensed in the US there is not an adjuvanted flu vaccine registered in the US nor any vaccine, as a matter of fact, against any infectious disease based on this new adjuvant; contrary to what is the case in Europe the US regulators will request to review ..result of ... development, like for any new vaccine because for them this vaccine will be completely new.

Now in terms of the capacity, again I would really like to avoid making any projections right now. When H1N1 started we said if the yields are as for seasonal, if full capacity is used and if each manufacturer can use its most dose-sparing formula for the vaccine, we may have as much as 94 million doses per week. This was a best case scenario and before we make any other projection we would really need to see what are the real yields because as I said, a few weeks ago we were seeing results indicating that the yields would be at best, only half and therefore you would have to divide total capacity by factor two. Now we are hearing that it is getting better so instead of changing prospects every day or every week, we prefer to stay on this best case scenario and to give a much better and really firm response when the yields are known and also when there is a confirmation of the efficacy of the vaccine which are tested right now.

HARTL: Thank you very much. The next question is from Martin Enserink of Science Magazine.

ENSERINK: Thank you for taking my question. I actually have two that are related. First of all I wonder do you prefer, as much as possible, adjuvanted vaccines to be produced and used and if so, what ways do you have to encourage countries and vaccine manufacturers to do that. Secondly, you have said in the past that ensuring supply for developing countries is one of the top priorities for WHO. Where do you stand on that because there have been very hard facts announced about that?

KIENY: In terms of adjuvants, of course as WHO has already said and stated, we have reviewed the safety of adjuvanted vaccines as they have been tested for H5 and also, as they are used and now more than 40 million doses of adjuvanted flu vaccines have been used in Europe already, so we see no apparent safety signal and really think that the Organization, based on expert advice - this is not the Secretariat opinion, this is based on expert advice - that there is no safety concern with using adjuvanted vaccines. As I said, of course, there will be side effects. People will have sore arms and may have dizziness and there may be more rare severe side effects but there is no signal to that for the time being. So, manufacturers will use adjuvanted vaccines, there is no doubt they are producing those and they will be used in quite a number of countries and even the large



users of vaccines will be testing and consider using adjuvanted vaccines when they have been tested in clinical trials.

Now in terms of availability for developing countries, as you say, WHO is really trying to ensure that all countries, including developing countries, will have access to vaccines. So, the recommendation that we had from our highest advisory body on immunization on 7 July, the Committee is called SAGE - Strategic Advisory Group of Experts - WHO has made the recommendation following the SAGE meeting that all countries should immunize, at the minimum, their health workers. We are in line with this and are discussing with manufacturers about having access to their production capacity, either through donation or through access real-time to their capacity at a reduced price, at a more affordable price on behalf of developing countries and we are really striving to make sure that the quantity of vaccine that WHO will be able to access directly, not talking about what the countries negotiate themselves, will cover at least these populations.

In terms of donations, we have had two generous donations as you know - one for 100 million doses and the other for 50 million doses. We are discussing with other manufacturers but all the manufacturers are really looking forward to having better knowledge of the yields and therefore of what the real capacity will be before committing to a donation but we are confident that the vaccine that we will be able to acquire as I said, a vaccine to distribute to all countries, not to cover the whole population of course.

HARTL: Thank you. The next question is from Mr Gailano from Dow Jones.

GAILANO: I was wondering if you could give us a bit more details of what kind of side effects we are looking at, if they were to occur and also if you could maybe elaborate on the probable time that will elapse between the first results and the actual deliveries of the vaccine, presumably towards the end of the year. Thank you.

KIENY: In terms of side effects, what will be monitored are the usual side effects of the vaccines which, as I said are fever, pain, nausea, diarrhoea, fainting. In addition what we will really look with great scrutiny by all involved in post-marketing surveillance will be what is called Guillain-Barré Syndrome, which is a very rare side effect which happens sometimes after vaccination. It is not something which has been described for seasonal influenza vaccination. It has been described in one situation which was in the 1976 vaccination against Swine flu in the USA but even there it was a very rare event - 30 people died out of 40 million people immunized. This is always a tragedy there is no doubt but we are discussing 30 people as compared to 40 million vaccinated. Because of this event, the causes of which only are only starting to be understood and not completely, all the post marketing surveillance will certainly be very wary of this possibility of this Guillain-Barré Syndrome and will follow this very closely and a procedure put in place in countries to be sure that even in low income countries it will be possible to detect this side effect very early. Now, in terms of availability for use, as I said it will depend on the



regulatory decision if regulators license, as we think it is likely, the vaccine in September it may be the case that some countries may already start vaccinating in September.

HARTL: Thank you very much. The next question is from Signor Ezzekial Ignoguran from La Razon in Argentina. Go ahead please.

IGNOGURAN: Thank you. I want to ask if there will be any kind of support programme for developing countries to get the vaccine.

KIENY: In terms of support for procurement of vaccines, yes, as I tried to explain, WHO is negotiating with the manufacturers to have access to vaccines for developing countries and this is through donations or purchase at a reduced price so we will assure a minimum level of coverage in all low-income countries. In terms of countries in the Latin-American region, as you know, there is a mechanism which is in place called the PAHO Revolving Fund by which the Pan-American Health Organization procures, buys vaccines on behalf of Latin-American countries. Our colleagues at the Pan-American Health Organization are already also discussing with manufacturers the purchase of vaccines for the Latin-American countries in terms of covering the population with H1N1 vaccines so I would really encourage the Latin-American countries who are not yet in contact with PAHO to contact this organization.

HARTL: Thank you, the next question is from Deutschland Funk, go ahead please.

DEUTSCHLAND FUNK: I would like to know how similar the vaccines which are now under development are to the vaccine from the 1976 vaccine in the US which caused Guillain-Barré Syndrome problems.

KIENY: The vaccines are very different. Of course they are also similar in the sense that both are made out of influenza virus grown in eggs so this is the similarity. They are very different in the sense that the degree of purity that is obtained now with the vaccine which is used now both for seasonal and with the use of pandemic vaccination was much less advanced in 1976 so there were very many more impurities in the vaccines. I must say also that for people who sometimes who are worried about association of adjuvants with Guillain-Barré that at time in 1976 the swine flu vaccine which was associated with the Syndrome was not adjuvanted so, yes, they are similar in the sense that they are all influenza vaccines but their formulation, what they are made of, and the impurities which are present in today's vaccine, the modern vaccine, is much less than what we had 30 years ago. So the vaccine that we have now is much purer and the quality controls and testing in the laboratories which is made on today's vaccine is much better than that of 30 years ago.

HARTL: The next question is from Helen Branswell from Canadian Press.



BRANSWELL: Dr Kienny, you were talking about the fact that there could be some temporal associations drawn between the vaccine and things that happen to people after they get it. Right now vaccines are undergoing a lot of scrutiny, there is a lot of scepticism about them in some very affluent societies, such as the US and the UK. Are you concerned that this mass vaccination campaign could actually create problems for the reputation of vaccines?

KIENY: We hope not because vaccines are really one of prevention methods against infectious diseases which is the best in terms of efficacy, the safest and really we are always worried when there are rumours of vaccine safety and most times, these rumours are unfounded so it needs to be reacted to very quickly. This is why we hope that by the time that the vaccine will be implemented we will have everything in place at least in the first country which vaccinates to make sure that sickness can be picked up very early and also that any cause of an adverse event, apart from vaccine, can be found as quickly as possible so that these cases of side effects, which will occur as I said, can be explained. I think we will have to work very quickly in detecting them, explaining about them and communicating to the press and we hope that we will have the assistance of the press to help us dissipate, when it is appropriate, as soon as possible these rumours about vaccines being unsafe.

HARTL: Before we go to the next question, can I thank journalists for having come on line today and let you know that we unfortunately only have time for a few more questions. The next questions is from Bob Rose of Telegraph News Service.

ROSE: I was wondering if in some countries, such as the US, if people may be getting seasonal flu shots and the H1N1 vaccine at the same time or possibly in quick succession and if there is any concern about the reaction to the seasonal vaccine, dampening the immune response to the H1N1 vaccine antigenics and I wonder if there is much concern about that.

KIENY: I don't think that there is concern for the time being so the population that for receiving seasonal vaccines and the first time of receiving H1N1 vaccine are not completely overlapping - they are in a sense but not completely so it is not at all a fact that a person will receive the two vaccines on the same day and then we will have to follow up to see what is the immune response but for the time being there is no cause for worry especially for vaccines because the influenza vaccines are really vaccines which are very well known in terms of the seasonal use of these.

HARTL: The next question is from Mr Schmidt of Der Spiegel.

SCHMIDT: There have been specific concerns raised about the adverse events in pregnant women especially because there has not been a lot of testing of vaccines on pregnant women obviously. Are there any plans to use non-adjuvant vaccines in this kind of group?

KIENY: As you rightly point out there is no experience with using adjuvanted vaccines on pregnant women - there is a lot of experience of using a seasonal non-adjuvanted vaccine so to answer your question I would like to refer to the recommendation of SAGE on 7 July where it says that in view of the fact that pregnant women seem to be a group at risk of more severe adverse events and potentially of death with the H1N1 pandemic, the recommendation of SAGE was that pregnant women should be considered as one of the priority targets for vaccination and SAGE goes further in saying that in countries where un-adjuvanted vaccines are available these used be a priority use for pregnant women but that in countries where there is no availability of un-adjuvanted vaccines then governments should consider using what is available in the countries, which means either live attenuated or inactivated adjuvanted vaccines in view of this benefit.

HARTL: Next is Mr Uoro of CTV Canada.

UORO: I have a question about whether the vaccine's safety will be profiled in those who have already had the disease. There are a lot of patients who come down with this disease but do not actually have the symptoms based on the data from Peru. This sort of follows into another question which is, what is the progress in the development of serology, that is to say blood tests, in determining past exposure and also better determining case fatality rates of this disease based on many who may have been exposed and not realised it.

KINEY: In terms of testing the vaccine first in those who have already been infected by the virus I think there is no plan to do that so the vaccine is being tested in normal healthy volunteers without exposure to the H1N1 virus so far and I do not know of any plans to test it in previously exposed persons. Development of the diagnostic test is of course on-going. I do not know either of any plan for testing people before giving them the vaccine and actually, such a test would be very costly, delay vaccination campaigns and there is no reason, based on safety, why this should be done at this stage. There was another question.

UORO: Do you foresee a safety concern in giving someone the vaccine if they have already had the disease and should there not be careful monitoring to make sure that giving the vaccine to someone who has already had the disease does not have an untoward or increased risk of side effects?

KIENY: There is absolutely no reason to think that somebody who has had the disease already have any adverse event following immunization and this is based also on experience with other vaccines including influenza vaccines. So these adverse events will be monitored very very closely and yet it appears that the detection of somebody who had the disease and then had the adverse event, will be investigated very closely but for the time being there is no concern regarding this point based on previous experience with other influenza vaccines of course.



HARTL: The last question today is from Agence France Press here in Geneva.

AFP: Greece announced that they are planning to vaccinate the whole population. Do you think this is realistic and do you suggest to governments that they should do the same since there is not enough vaccine.

KIENY: What SAGE has said is that they have given a recommendation to vaccinate at least the health workers and then has listed a number of groups which are potential targets for vaccination according to the strategy of the country and this is really a government priority to see what they want to achieve with vaccines or with using an antiviral or with use of other prevention or treatment methods. Some countries have decided to vaccinate their whole population - there is no indication that this would be unsafe so it is again a strategy of a country to protect its population against influenza pandemic. Not all countries which could have access to enough vaccine have chosen to do this, again it is a choice of strategy which is the country's choice.

HARTL: Thank you very much again Dr Kieny. This has been the virtual press conference from WHO Geneva Headquarters for 6 August 2009 and thank you to all the journalists online for having participated. A final reminder - the audio file will be available shortly on the website and a transcript will be available later. Updates are always available on www.who.int. Thank you.