Transcript of virtual press conference with
Kristen Kelleher, Communications Officer for pandemic (H1N1) 2009, and
Dr Keiji Fukuda, Special Adviser to the Director-General
on Pandemic Influenza, World Health Organization
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Kristen Kelleher: Good afternoon. This is Kristen Kelleher speaking from the World Health Organization in Geneva, Switzerland, today on Thursday, 26 November. This is our weekly virtual press briefing. Today I have the pleasure of welcoming Dr Keiji Fukuda, the Special Adviser to the Director-General on Pandemic Influenza. Dr Fukuda will make opening remarks and then we will open up for questions. Dr Fukuda, over to you.

Dr Keiji Fukuda: Thank you Kristen. Welcome everybody. Thank you for attending this virtual press conference. As has been normal in our earlier press conferences, what I'll do is try to provide an overview and highlight some main subjects and throw it open for questions. So the thing I want to do is simply give an update on how the pandemic is progressing.

So currently we see that the pandemic continues to evolve, primarily in the northern hemisphere. However, overall the health and surveillance systems out there appear to be coping quite well. Now, activity remains high in a number of northern hemisphere countries and, as we have previously reported, low in the southern hemisphere. There continues to be changes in up and down activity in countries but I think that overall right now it is still too early to say whether we are seeing peaking of activity in the northern hemisphere. Again we see differences on a country by country basis but difficult to say on an overall basis. I think the take-home message here is that we need to expect to see continued activity for at least some number of weeks in the northern hemisphere before we see a definitive downward turn.

Now the second point I want to make is that we now have about seven or eight weeks experience with the pandemic vaccination programmes out there and that pandemic vaccination is proceeding with no unusual safety problems identified to date. So, right now we estimate that about 40 countries have distributed at least 100 million doses of vaccines among their populations. The rates of local side affects, such as soreness in the arm or some redness, is, as expected, about at the rates of the seasonal vaccine or perhaps even lower. We have seen that there has been some reporting of serious events in investigations of people after they have been vaccinated and in most of these investigations we have seen that the serious events are not related to the pandemic vaccine. Yesterday, the Canada Public Health Agency reported that there were six cases of anaphylaxis with one lot of pandemic vaccine. Now, as we understand, none of this vaccine was distributed outside of Canada. All of the persons who developed anaphylaxis recovered fully and did not require hospitalization. All of the unused doses of vaccine have been put on hold - that is, they are not being used at this point while investigations go on. One of the take-home messages here I think is that this is exactly how we hope for the safety surveillance to go on. This is an instance in which a problem was

identified, both by the country and by the company and it was quickly acted upon. The information was gotten out and the appropriate steps were taken.

The third point that I want to make is that in the past week or so we have had some potentially important developments that I think are important to put in context and to understand. One of these has to do with two separate clusters of oseltamivir resistance identified in the UK and in the United States, again separate clusters and the second event is the reports of mutations that have received a lot of publicity in the media. So, let's first turn to the clusters of oseltamivir resistance. Towards the end of last week - let me first start here - at this current time WHO has been notified of about 75 oseltamivir resistant viruses. Now among these 75 oseltamivir resistant viruses, at the end of last we have two clusters of viruses which were reported to WHO. Now, in the United Kingdom we understand that there were nine patients in a hospital who developed pandemic illness and we understand that from five of these patients, oseltamivir resistant viruses were identified. In one of the patients the virus was sensitive and in the three other viruses the tests are still going on.

In a separate cluster in the United States we understand that there are four patients in one hospital in the United States who also developed pandemic illness while hospitalized and they also had oseltamivir resistant viruses isolated from those four patients. Now, similar in both clusters are a couple of important points. These clusters of oseltamivir resistant viruses were isolated from patients who have severe immuno-compromising conditions. These people were in immuno-compromised conditions either because of their underlying disease or because of treatment for their disease. Now, at this point, investigations are under way and WHO is in contact with the investigators but even while we wait for further details from the investigations, there are some points that we want to highlight. First is that to date most of the oseltamivir resistant viruses that have been identified in association with this pandemic, have come from sporadically occurring cases of disease. In this instance, we see two reports of clusters of oseltamivir resistance and this raises the question of whether we are seeing a change in the epidemiology of these viruses. The answer right now is that we don't know the full answer but it is more likely that we are not seeing a change, a major shift in the epidemiology or in the properties of these viruses with regard to oseltamivir resistance. So, right now we think that there probably is not a major change but this is why the investigations are going on in part. However, it does highlight that we do have particularly susceptible groups of patients out there, which again underscores the need for why surveillance is so important.

Now, in the second point that I wanted to make here is that most of the oseltamivir resistance that we have seen to date has arisen in association with the use of these drugs for prophylaxis but in this instance we have seen oseltamivir resistance develop in the face of treatment. Again it brings up the question, are these drugs being less effective in treatment. The answer here is that in fact to the contrary, most of the input that we are getting from clinicians around the world leads us to think that these antiviral drugs, when they are used appropriately and used early, are in fact reducing the number of serious outcomes and so they remain highly effective when used right. But, these clusters also point out that there are some unusual situations and people with severe immuno-compromising conditions are the most susceptible people out there. So, in the treatment of these patients we have to be ever mindful about how they are doing and how these drugs might be used. Now, one of the things that I do want to specifically address is that these are severely immuno-compromised people. There are people with milder forms of immuno-compromised states, for example, large numbers of people with HIV infection. Right now we do not see any evidence of a large impact in immuno-compromised people with milder forms and we do not see a large impact in HIV infected

populations so again I want to stress that these clusters have been reported in people who have very severe immuno-compromised states.

The bottom line here is that treatment remains effective and in fact, there is growing evidence of their effectiveness but we do have to be vigilant in these very susceptible people.

Now the last point that I want to address before I throw it open to questions is that in the last several days we have also seen a lot of reports in the media about a mutation and this was specifically raised because it was Norway which recently reported seeing mutations in three patients who had severe disease. Since then there have been additional reports of the same mutation being seen in viruses in a number of other countries, such as Brazil, China, Japan, Ukraine and the US **[CORRECTION FOR ACCURACY: AND MEXICO]**. The question is whether this mutation again suggests that there is a fundamental change going on in viruses out there or whether there is a turn for the worse in terms of the severity. I think that the answer right now is that we are not sure. I want to answer why we are not sure in a way which explains why more investigations are needed. As you know these influenza viruses change frequently. Their gene properties change because these are viruses which frequently undergo mutations and so mutations in and of themselves are not necessarily important and in fact, if every mutation was reported out there, it would be like reporting changes in the weather - saying that there is a temperature difference of one degree one hour and then an hour later, saying there is a temperature increase or decrease of one degree. This kind of information does not really help anybody. But, what we try to do when we see reports of mutations is to identify whether these mutations are leading to any kind of changes in the clinical picture - do they cause more severe disease or less severe disease and also we try to look at whether these viruses are increasing out there, suggesting that there may be a change in the epidemiology. With this particular mutation we have seen that it is reported in people who have severe disease and we have also seen that it is also been reported in people who have milder disease. Right now one of the questions is, is it really associated with severe disease more often. The second point that though, is are these viruses becoming more common or are they relatively infrequent. So again, this requires looking at more viruses over time to get a sense of whether there is a change in the overall prevalence or number of these viruses. It is these kinds of investigations which require time and it is these kinds of questions which have to be answered before we can fully talk about the importance of one mutation or another mutation.

Le me stop there and throw it open to questions. Thank you.

Kristen Kelleher: Thank you for the opening remarks Dr Fukuda. Before we go to questions I want to remind everyone listening that an audio file of the broadcast will be available immediately after this briefing and a written transcript will be available later on the WHO website at www.who.int. Again, for journalists who want to ask questions, please type 01 on your keypad to get into the queue. Now for the first question, it is from Helen from CNN Medical News **[CORRECTION: MARION FALCO]** .

Marian Falco: I have two quick questions. Can you tell us about the ages of these immuno-compromised people who showed resistance to Tamiflu. Can you explain to me why WHO does not consider all children to be a high-risk group. Last week in the briefing it was mentioned that for countries who think that children are in a high-risk group. Here in the US all children and young people up to the age of 24 are considered high-risk. I am not clear why that is different with the WHO. Thank you.

Dr Keiji Fukuda: Thanks for these questions. In terms of the ages of the patients, I do not have that information. I think there are a lot of specific details about the investigations and the

patients and the conditions that will be reported by the investigators but we don't have that information here. In terms of your second question why are all children not considered to be at high risk, when we talk about high risk what we mean are which groups of people are at highest risk for developing severe disease or complications and this is based on seeing what the effects of the infection are in different groups. So, based on the information that we see right now, it is clear that in children under five years, they are the ones who are hospitalized most often and then when you go up the age ladder, you see that the hospitalizations and complications occur less frequently and so, depending on the information that you have, different groups might make different cut-offs in terms of the age of risk but I thing that it is clear that the very youngest children are at higher risk for being hospitalized with severe complications and that the risk for those events decrease as we get older. Thank you.

Kristen Kelleher: Thank you Marion. The next question is from Helen Branswell of the Canadian Press.

Helen Branswell: Thanks very much. Keiji. In your opening remarks you said that you think that it is going to turn out to be unlikely that the clusters of resistant cases are a signal of the changes in the epidemiology of the virus. Can you explain why you think that is and also I was hoping you could address a situation that has arisen in the United States - I don't know if you have seen it yet but there is a report of a paediatrician from West Virginia who tested positive for the virus twice - she got sick in August and again in October**.** Her tests were confirmed by CDC. Is it thought that this is really a sort of an outlier, you know a one in a million type of thing or is anybody looking at the possibility that immunity to this virus might be so short lived that people could get sick multiple times in a short period of time.

Dr Keiji Fukuda: OK thanks Helen. Again, let me address the first question first. In this particular instance we are looking at clusters of oseltamivir resistant viruses take place in fairly specialized settings so these are hospitals taking care of very immuno-compromised patients and if these viruses in this situation do not spread into the community spread out more widely again what is point out is that there needs to be a lot of vigilance taken with those groups of patients but probably does not have a big implications for the overall patterns of illness in the general community. However again like all new observations it is something we have to keep on top and watch out and make sure we don't see this is a spreading phenomenon. Now in terms of your second question, I have not seen specific reports I have seen mentioned of this person who has infected twice. In general with influenza infections most people who become infected with influenza remain immune to infections for an average at least for couple of years and so it is unlikely that with the pandemic virus we are dealing with the completely new phenomenon in terms of protection. So again, I think that there are always some exceptions to rules but it is unlikely this is a very broad phenomenon. So I will be surprised if we hear about many cases such is this. Thank you.

Kristen Kelleher: The next question is from Vera Custis. Vera? [CALL DROPPED]

Let me take this moment to again remind journalists who want to ask questions to please type 01 on your keypad to get into the queue. We have another call on the line; it is Fergus Walsh, BBC.

Fergus Walsh, BBC: Thank you very much indeed. Here is my question. I am in a couple days ago the Health Protection Agency in England estimated that up to a third of school children may have had swine flu and also estimated that only about half of them would have had any symptoms at all so half of them were asymptomatic and I wonder whether any kind of work had been done internationally to give a sense of how much of the world's population has now had contact with this virus.

Dr Keiji Fukuda: I think that when we look at past pandemics you know we actually this question came up a number of times at the start of the pandemic and we look at past pandemics we have said that based on those that we can anticipate that over the coming year that we might expect a third or perhaps the more population to become infected by the new pandemic virus and so I think the estimates from the UK you know are in keeping with those kind of rates we have seen in the past. Again there are studies which are going on to look at the levels of antibodies in different communities and this will provide the most definitive information that we have but I think that we still need to see those kind of studies done at the end of the pandemic to know about what percentage of children of different age of groups getting infected. Thank you.

Kristen Kelleher: The next question is from Eliane Engeler from Associated Press.

Eliane Engeler: Yes. Hi. Just a question about the numbers of oseltamivir-resistant viruses you mentioned in your introduction, that there were 75 viruses and I understand that means 75 patients, and then you mentioned 4 patients in the US and I think 9 in the UK, so where are the others, and is it really viruses equal the persons? And secondly I am not quite clear about the report mutated cases of flu in China. Were the same mutations as were seen in Norway and in Brazil and other countries? Thank you.

Dr Keiji Fukuda: Let me take these 3 questions. But let me first clarify in the UK there were 9 patients who became ill with pandemic influenza. From those 9 patients, 5 of them have oseltamivir-resistant viruses, 3 of those patients the testing results are going on. In 1 of those patients 1 virus was found to be sensitive. So anyway 5 viruses from that cluster. The other viruses do come from different individuals that have been reported from the start of the pandemic. So in general these other viruses come from people who have developed resistant viruses again in many instances they have developed resistant viruses because they were taking prophylactic doses of oseltamivir and not treatment doses of oseltamivir. So anyway these have been viruses which have been seen since the early part of the summer when the pandemic first started. And in terms of your question, yes the mutation that I am talking about in the countries that I mentioned, and you asked about China specifically, but also the other countries you are talking about, the same mutation that was seen and reported in Norway. Thank you.

Kristen Kelleher: Next is Mr. Mitamura from NHK.

Mr. Mitamura: Thank you for talking my phone. I would like to ask again about the cases of vaccines side effect in Canada and so the rate of side effect in Canadian cases are not unusual compare with these seasonal vaccines cases. Is that correct? One more things I would like to ask is that the mutation virus, when did WHO had found the first case of this mutation? Thank you.

Dr Keiji Fukuda: OK. In terms of the rates of anaphylaxis. Yes the rates reported by Canada overall have been quite low and so that is the reason why the report of the 6 cases from one lot of vaccine stood out and so than they identified by that number. And again in general the rates of anaphylaxis reported for vaccination overall in Canada have been very low. In terms of the mutation, now this is a mutation which historically had been identified as I believe, many years earlier, this is a mutation at the position called 222 in the [….] gene. I do not know exactly when the very first mutation was identified in this current pandemic virus but we know that from the cases identified in Norway the first identification of this mutation in Norway was earlier in the summer. So sometime around June or July with the second mutation being identified later in the summer. So otherwise right now I don't know when the mutation was first identified worldwide among the pandemic viruses. We would have to get back to you on that. Thank you.

Kristen Kelleher: The next question is from David Brown at *The Washington Post*.

David Brown: Hi. Thanks a lot. Dr Fukuda, as I am sure you know, there's been some reports that the epidemic is peaking in regions of the United States and starting to fall off. I am wondering is there is any good explanation for why it doesn't just run through the population, all of the susceptibles, and then decline, but why it would peak, you know really in optimal flu season, and then presumably come back in a couple of months.

Dr Keiji Fukuda: Good question David. That is a difficult question, but one of the general observations about all infectious diseases like influenza is that when you have outbreaks they generally peak and then begin to decline before everybody who is susceptible in that population gets infected. And I think that if we think about, you know, these populations of people, you know people have contact with other people, and so if a person who is not protected runs into somebody who is infectious they get infected. But if after a while you have enough people infected, and then they become protected, you will see that chances for running into people who are susceptible begins to go down, and that's when you begin to see the decrease in infections going on in a population, and eventually it goes down low enough so that you still can have susceptible people out there who could potentially become infected, but in that current epidemic or that current episode do not become infected, and then later on as time passes again the conditions change for whatever reasons, and then it is possible for the virus to get reintroduced. Overtime with influenza we see that it occurs partly because the virus itself changes, which means that it begins to escape the immunity which is built up, but I suspected it also has to do the fact that people are not static, and populations are always mixing, and so the mix of protected people and susceptible people also changes. It is quite a complex phenomenon that we see over and over again with these influenza epidemics.

Kristen Kelleher: We have time for just a few more calls. The next call is from John Zaracostas, BMJ Geneva.

John Zaracostas: Good afternoon Dr Fukuda. Was wondering if you could elaborate, sir, if the immuno-resistant cases were suffering from cancer, tuberculosis or advanced cases of AIDS. Also with reference to anaphylactic shock in Canada. Is the substance that triggered the allergies benn identified yet? Thank you.

Dr Keiji Fukuda: So John. I don't know all of the conditions that led to the patients being immuno-compromised. I understand that many of them had malignancies, more specifically hematologic malignancies. So these patients were also under treatment which again can further compromise your immune system. But again I don't have a further breakdown of what specific conditions led to their immuno-compromised states.

In terms of the specific substance or why people developed anaphylaxis, I think this is a very important point. I think when we hear about cases of anaphylaxis then the immediate temptation is to jump and think about the vaccines. Is something wrong with the vaccines? In fact, this lot of the vaccines was about a 172 000 doses of vaccines and much of that vaccine was administered to many people, most of whom developed no reactions at all. And so the number of people who developed anaphylactic reactions who are really quite small and so I think it points out there is some combination of factors involving both the persons and then what they are exposed to the pandemic vaccines. So it may be that in fact this pandemic vaccine is exactly the same as every other lot of pandemic vaccine out there but it happened to be given this group of people who for whatever reason were more prone to developing anaphylaxis. So I think these are again complicated issues to be teased out. This is why these kind of investigations are done. Thank you.

Kristen Kelleher: Our last question today will be from Gabriella Sotomayor from Notimex, Geneva.

Gabriella Sotomayor: Thank you very much Dr Fukuda. There are some reports of H1N1 linked into a rise in bacterial pneumonia cases. If you could comment on that and, secondly you mentioned several countries with the mutation cases but I am not sure if you mentioned Mexico, if you could clarify that. Thank you very much.

Dr Keiji Fukuda: Thank you Gabrielle. Let me address the second question first. I don't know of any reports of this mutation being reported in Mexico. So it may be that we hear of such reports later on but right now I don't know of any such reports. **[CORRECTION: VIRUS MUTATION HAS BEEN OBSERVED IN MEXICO. SEE EARLIER PANDEMIC INFLUENZA BRIEFING NOTE 17 OF 20 NOVEMBER AT http://www.who.int/csr/disease/swineflu/notes/briefing_20091120/en/index.html]**

In terms of your first question, one of the ways that influenza typically makes people sick is that you have an influenza infection and then after that influenza infection occurs, it is followed by a secondary bacterial infection and in fact, this is the way that seasonal influenza often makes people sick and leads to pneumonia. One of the surprising things about the pandemic influenza virus is that many of the serious cases and many of the fatalities that we saw, were a result of the virus directly attacking the lungs and causing a very serious illness. However, it is true that we have now seen more reports in which people do not necessarily have serious disease directly from the virus itself alone but that people have developed secondary infection, such as staphylococcal infections or streptococcal infections which are common bacterial infections that can follow influenza. So, we see this more often, we see this reported more often. Again I think this is not a surprise, this is what we often see with influenza. I think the bigger surprise was that we did not see more of these reports earlier in the pandemic. Thank you.

Kristen Kelleher: Dr Fukuda, thank you very much. That will conclude the briefing today. To remind you, an audio file of this briefing will be posted immediately after the briefing on the WHO web site at www.who.int . And a written transcript will be posted on the web site later. So thank you all for listening. And thank you to Dr Fukuda.