

**EWSI**  
**Pre-pandemic Preparation Workshop**  
**Stanhope Hotel, Brussels**  
**23 January, 2009**

*Edited Minutes*

**Morning Session: Introduction**

ESWI's half-day workshop to explain the necessity of pre-pandemic planning to EU and national research and policy officials began promptly at 11:00 am and was introduced by its chair, Dr. Ab OSTERHAUS of Rotterdam's Erasmus Medical Center.

Noting that the workshop's content was an extension of ESWI's Third European Influenza Conference that took place in Vilamoura, Portugal in September 2008, he said "we now want to inform those involved in policy-making. There are a lot of planning tools available, even if there is a lot of confusion in Europe about what to do regarding anti-viral stockpiling, for example, where each EU member state is going for its own solution."

"We want to show you the tools and how to use them. We also want feedback about what is happening in your respective countries. Afterwards, we'll publish the outcome of this meeting, perhaps including an editorial in *Vaccine*."

Osterhaus reminded participants that all the workshop's speakers have been involved in pre-pandemic planning in their countries. "Thus, this is a good opportunity to bring them all together for your benefit," he said, adding that "we decided to keep this a closed meeting – not inviting the press *and* not inviting any individual companies."

**First speaker: morning**

OSTERHAUS opened the first session with a quick summary of the issues to familiarise EU policymakers and other officials in the room with the technical and virological fundamentals of pandemic risk.

*His remarks:*

Noting that virus strains are split between seasonal (H3N2, H1N1, etc.) and avian influenza ones (H7N7, H5N1), he said this distinction "is continuously mixed up" by the press.

All the HA subtype divisions of influenza A (16 types) and NA divisions – there are nine – have been discovered and they're all in birds. Only those with specific amino acids (H5 and H7) are the high pathogenic ones to worry about and they are in poultry; all the others are found in wild birds but are low pathogenic.

There are two theories by which an avian virus can become a pandemic. One is genome reassortment where viruses mix and exchange their genomes – in a bird or pig, for example. This happened with the 1957 and 1968 Asian flu outbreaks.

The other involves sequential mutations, followed by a virulent strain's gradual introduction into bird or pig until it becomes transmissible. Example: 1918 Spanish Flu pandemic.

### **What is the situation today?**

Influenza A virus. There are recent zoonotic transmissions, with it being identified for the first time in 1997 in Hong Kong: the now well-known H5N1 virus.

There have been almost 400 cases of human contraction of H5N1 during 2003-2008 of which 250 died from the disease. Moreover – and this is not reported by the press – every week there are people in southeast Asia who are dying from the virus.

#### *How are the viruses spreading?*

We think it comes from migratory wild birds. Mallards can be infected, but not die and thus spread the virus. While these viruses spread easily between animals, they do not between humans. Human viruses tend to attach to the upper respiratory tract, while avian viruses tend to concentrate in the lower tract. We know this about these viruses however: that one of them is going to be responsible for a pandemic.

#### *What interventions strategies are needed?*

Surveillance, antiviral therapy and vaccination.

Osterhaus said surveillance in Europe is exemplary and, regarding antiviral therapy, that seasonal treatment is key. "Seasonal vaccination is the most important strategy."

#### *What are the key issues surrounding vaccination?*

Response time generally takes around 6 months—that's too late—and global production capacity currently stands at 400 million doses world-wide.

#### *How can we do better?*

Improve production systems, for example. Instead of relying on slow and expensive chicken-embryo based vaccine methods, we could go for cell system technology or seed-strain preparations or reverse genetics: this will gain us a month in time.

#### *But which strain selection to use?*

I think the future lies with adjuvants – the substance added to a vaccine to stimulate the immune system's response. We've looked at alum, and the MF59 and AS adjuvants because some of these have been licensed, meaning they've been tested in humans and animals.

#### *How to deal with these vaccines?*

We do not know which virus will be the basis of the next pandemic. So which vaccines to buy and stock? Public policy officials need to think about vaccine strategies and the difference between pre-pandemic planning vs pandemic planning. Sitting and waiting is not an option.

**Second speaker: morning**

Dr. Neil FERGUSON, director of outbreak analysis and modeling at London's Imperial College, spoke about modeling and risk assessment techniques.

*His remarks:*

He outlined the factors contributing to a pandemic such as methods of transmission related to modern travel modes, (air travel, etc) and the mix of combined interventions to slow its spread (school closures, quarantines, etc.).

Ferguson offered his audience an example simulating the spread of a European pandemic. "We would expect a pandemic to peak in 8-12 weeks after its first case. The response to it will not be synchronized across Europe, either within a country or between them. You'll see a rate of 15 percent or more local absenteeism in the first week."

*What about clamping down on borders as a preventative measures?*

It was used during the SARS outbreak in Hong Kong [in 2004], but with little effect. The problem is the sheer rate of growth of a pandemic. Your case number will grow by tenfold every 1-2 weeks. Thus, travel restrictions won't stop its growth. Even if you stopped 99 percent of all travel, which would be severely disruptive for a modern economy, it might slow down the spread by only 2-4 weeks. Restrictions are only useful very early in a pandemic.

As for border screening of people with identifiable symptoms, this is ineffective since it spots only symptomatic victims: by then it's too late to halt the spread of transmission.

*What about mitigation and the benefits of combining interventions?*

There is a sort of "failsafe policy" if you target things twice, for example. Some interventions could target susceptibility and infectiousness or infectious contacts. Where? Homes, schools, communities, etc. The big benefit of school closures is the reduction of peak incidence—by as much as 40 percent—along with the possibility that it could also prevent one out of seven cases. But it is difficult to execute: closing schools for 12 weeks would create huge child-care problems.

**Morning Session Q&A***Question*

Hans HOUWELING of the Netherlands' Health Council. "Are H5 and H7 pathogenic for birds only, or do they apply to humans as well. And what about pigs? In the past they played an important role, no?"

OSTERHAUS: "It's not just the H5 and H7 subtypes. H9 is also pathogenic to birds, though not as severe. When we are talking about pathogenicity for humans, we have only scratched the surface. That said, we know there are a number of pathogenicity markers for humans that do not correspond to those for birds.

The patterns and rates of transmission are different, too. An important point is that if we look into H9 viruses, there have been some people who have died from it. If H9 was

the basis of the next pandemic, it could become a weak pandemic similar to 1957 or 1968. However, we cannot predict that. Avian non-pathological viruses could be the basis for human infection. It's one of the reasons that in the framework of European research projects, a lot of work is being done in bird surveillance: we're building a repository of viruses that could be used later to fight pandemics."

As for your question about pigs, well let's say that more cats have died from H5 than humans. We have looked into the situation in pigs and it is not dissimilar from what we see in humans: no pig-to-pig transmissions, which suggest that the viruses' role in past pandemics may have been overplayed. There is a risk that if cat-to-cat or canine transmission takes place, then this might happen."

*Question*

Michael KUNZE of Austria's Institute of Social Medicine: "I am pro pre-pandemic planning, and our pandemic plan is based on cell culture. We hear people say they don't need an adjuvant. I would also suggest that we organize this meeting for politicians. They will have a different view on things."

OSTERHAUS: "I can tell you that ESWI is working on that idea [i.e., convincing politicians] quite intensively. We have contact with MEPs [Members of the European Parliament] and with national politicians. But it is they who have to decide at the end of the day, and they will only act at the request of their constituencies. If the latter are not prompted, nothing will happen."

This entails a three-layered approach, he said. "The first layer is convincing the public at large of the need to be vaccinated, and that's within ESWI's strategy. The second layer involves those professionals who can influence the politicians. And this includes health care workers: they are our major allies. But if they are not convinced that seasonal and pre-pandemic vaccinations are important, we have a problem. And the third layer is the policymakers and politicians themselves."

FERGUSON: "The challenge of getting politicians into the same room is a big one. The World Economic Forum in Switzerland might be one avenue to go down, however."

*Question*

Alexander KEKUE of Germany's Institute for Medical Microbiology, asked whether during the first wave of a pandemic there would be any matched vaccines. "Many people think it's possible to prepare the vaccine fast enough to save many. True or not?"

FERGUSON: "The big uncertainty is seasonality. If you see a nascent pandemic in southeast Asia in May, we could be lucky and not see any substantial spread in Europe until October, which gives enough time. But if it blooms in the beginning of October or November, then it would be with us in a month or two."

*Question*

KEKUE: “You’re building up a seed panel: how would you use this?”

OSTERHAUS: “We are still seeking funding to do this. But with the H7 virus we have shown that we could make a seed virus in 2-3 weeks. What we’re considering is a panel of seed viruses that can immediately be used to replace antigens that have already been stockpiled. If we have an H5 pandemic, vaccines are not geared to them. But if you look at the adjuvant-enhanced vaccines, they do offer rather broad protection. It’s a tough ‘and/or’ choice, however. Take countries like Sweden or Japan that stockpile H5 vaccines: if they don’t have an H5 pandemic, they look pretty stupid for the effort and cost. One solution could be: stockpile your antigens and adjuvant vaccines separately. Thus, if you see H5 emerging, then by Stage 4 [of WHO’s six-phase alert-based Global Influenza Preparedness Plan] you use it immediately. If you have your seed viruses ready, you can gear up in two months.”

#### *Question*

Itamar GROTO of Israel’s Ministry of Health: “Can models predict a second wave [of infection] and see the effect of intervention on this wave?”

FERGUSON: “We don’t understand why there were distinct waves in 1918, for example, or how this might propagate during a spring wave, an autumn wave and so on. It was not seen so clearly in ’57 or ’68. The best guess is that we’ll have a single large epidemic rather than multiple small ones as in 1918.”

#### *Question*

Bram PALACHE of ESWI: “My impression is that many people believe the threat of a pandemic has been exaggerated and, unconsciously, that has put off the urgency of taking action. It is thus a mental exercise rather than one of doing the preparation. Your views?”

OSTERHAUS: “Basically, there will be another pandemic. I agree that among politicians there is this lax attitude today. But when we saw a couple of kids die in Turkey, then the Commission kicked into action. We need these small events, unfortunately to awaken authorities. If it’s H5-based, it’s going to be a disaster. If it’s H9-based, it may not be. We have the means to combat a pandemic but we have to inform the public and our politicians.”

Arnold MONTA of the University of Michigan, added: “Another approach in dealing with politicians is to link the importance of seasonal flu to pandemic control, and to stress that the same approach in preparation will mitigate both. That’s what we’ve looked at in the United States. But it’s tough: in many parts of the world they don’t recognize the importance of seasonal flu but do seem to aim for pandemic control at the same time. We have to recognize that it’s difficult to get politicians to recognize this. Also, politicians don’t like uncertainty when you have to commit large sums of money.”

FERGUSON: “The scientific community has been poor at conveying the nature of the risk the world faces. We don’t know what the probability of H5 jumping to human

species is. But we know that its pathogenicity is much higher. The fact that 60 percent of people infected with H5N1 die is a real eye-opener.”

#### *Question*

Anna LONNROTH-SJODEN of the European Commission’s DG-Research: “Sometimes R&D delivers surprising results such as the discovery that a huge proportion of seasonal flu was Tamiflu-resistant. What is the effect on modeling and genetic implications of this trend?”

FERGUSON: “We’re looking at this for modeling. We’re trying to understand this. It’s a key objective of an EU-funded project known as FLUMODCONT.”

David REDDY of F. Hoffmann-La Roche added: “What is the 274 mutation, which causes resistance to Tamiflu? It generally led to a less transmissible virus. However, in the United States it was accompanied by other mutations, which favour the fitness of the virus. In normal evolution you would expect this. Mapping so far has identified viruses that lack the 274 mutation. It could be antigenic drift in the virus that took on board a 274 mutation, which is not what you would expect normally. We don’t know what drove this process.”

#### **Afternoon Session: Introduction**

Prior to the session’s debate, Cornelius SCHMALTZ of EU Commission’s DG-Research announced that EU funds a number of influenza-related projects. “We’ve funded projects on seasonal, avian and pandemic research since 2001, and have spent more than EUR 100 million on these subjects...from basic virology to vaccines to modeling and public health policy.”

#### **First speaker: afternoon**

Dr. Arnold MONTO of the University of Michigan opened the session. He said it was sometimes difficult to identify the US approach to pre-pandemic preparation and implementation of intervention strategies “because of its size, the fact there are so many agencies involved and because so much money is being spent.”

Noting that the US Department of Health and Human Services has the lead in biomedicine planning, he said the three pillars of pandemic control – antiviral stockpiling, non-pharmaceutical intervention and vaccines – have moved quickly in the last four years in his country and elsewhere.

#### *His remarks:*

I propose two terms to avoid confusion:

- \* stockpiling means keeping antigens and vaccines in a stockpile to be used early when a pandemic begins

- \* pre-pandemic vaccination means vaccinating selected groups before a pandemic starts – during stage 3 [of WHO’s preparedness plan]

Countries have realised very quickly that stockpiling is necessary. Two things have held back pre-pandemic vaccination in the United States. One is concern about “original antigenic sin” – the idea that a vaccine virus will determine how you respond forever to subsequent vaccines. The other more important one is the lessons learned about vaccination for swine flu in 1976. For that reason, US will be slow in adopting a pre-pandemic vaccination strategy.

Re: non-pharmaceutical intervention: We paid little attention to this because we had antivirals and vaccines. The US has now taken a very vigorous approach to non-pharmaceutical actions.

Re: vaccines: A few years ago we thought that this strategy had to be based on non-vaccines for the first wave of a pandemic, and then followed by a two-dose schedule. That has changed since then. One of the reasons is that we have not had any high-path H5N1 viruses, which will make a big difference in the way the country reacts to it.

Re: Vaccine approaches: There has been a recognition in the United States that the amount of vaccine produced for seasonal production determines how much you will have for a pandemic. There’s only one manufacturer in the US (Sanofi-Pasteur) and there is concern about the nationalisation of supply in a pandemic.

Thus, there is emphasis on cell culture research and production facilities in the US as best way to ensure enough vaccines in a pandemic. Also, a recognition of the need for new approaches to antigen sparing. This is seen as a more flexible approach, though that is debatable in terms of the availability of eggs and seasonality.

Re: mix and match strategy: The US view is to stockpile antigens and adjuvants separately, and then mix them to use the virus that is most appropriate for a given pandemic. Alum is unpredictable and some say it is unreliable as an adjuvant. There is a lot more acceptance of cell-culture based vaccine work, and much more caution about adjuvants.

One thing the United States alone has done is to look at live attenuated influenza vaccines (LAIV). The problem, however, is that you can’t test it before a pandemic hits. Thus far, it has not been possible to get an LAIV H5N1 strain: it is not replicating in the human volunteers who have been given the vaccine. It could be a receptor problem or something else. We don’t know.

Re: antivirals: The US government has supported development of new antivirals due to worries about resistance in stockpiles. The US approach has been to stockpile fewer antivirals than Europe.

Re: non-pharma interventions: The United States has taken an approach really different from rest of world: it’s a major component of control, and is backed by mathematical modeling of the spread of the 1918 pandemic. Intervention strategies have been discussed with State governments and in many fora.

### *Conclusion*

The biggest change regarding vaccines in the last two years is our ability to use them in the early stage of a pandemic. Vaccines are being approved based on their antibody profile, while antigen sparing is no longer an issue. Manufacturing capacity is available.

The big question: when do you administer this? WHO is discussing to change its pandemic phases so that key one is phase 4: the time when human-to-human transmission is taking place. That should be the focus for new strategies concerning vaccines.

**Second speaker: afternoon**

Jonathan VAN-TAM, professor of health protection at the University of Nottingham, then took the floor “to touch on the more practical issues related to using antivirals and pre-pandemic vaccines.”

*His remarks:*

A virus can reach Europe from Asia in two-to-four weeks, so any screening at ports of entry will most likely be of very limited value.

Secure storage, yet compatible with rapid delivery (local/regional equity in distribution). Seasonal use too low to allow storage within community seasonal supply chain (true pandemic stockpile).

The public health purpose of antiviral use means it is perfectly defensible to limit antiviral use to HCWs [health care workers] or those across a country’s CI [critical infrastructure] sector. The question is: can other priority groups be identified in advance? And would these priority groups be ethically and publicly acceptable?

Re: the use of vaccines:

- \* a vaccine must have an established safety profile, and it must induce a fast, strong, long-lasting and boost-able immune response

- \* vaccine must also induce a wide breadth of immune responses for cross-protection. We know that there are as many as 10 clades against which protection must be offered.

- \* oseltamivir [Tamiflu] has an approved shelf life of five years in most markets, and there’s been a recent extension to seven years in US stocks; governments can choose to extend the shelf life of their stockpiles, based on these data. Roche is developing a method to extract active ingredients from expiring capsules for reinsertion into new capsules, thus ‘re-setting’ the clock on existing procurement.

- \* there isn’t a one-size-fits-all in terms of how a pre-pandemic vaccine (PPV) might be deployed.

*Conclusion*

Any decision to stockpile neuraminidase inhibitors is central to an overall package of pandemic preparedness measures.

Large numbers of practical issues must be considered to build an effective operational strategy. For example: it’s as bad to procure antivirals and then fail to deliver them as it is to have none at all.

Stockpiling or giving human H5N1 vaccine in advance of a pandemic carries risk associated with not knowing in advance what the pandemic virus will be. But it also offers huge potential benefits as ‘true’ pandemic vaccine is likely to be ‘post-pandemic’ vaccine.

## Morning Session Q&A

### *Question*

Alain VANDERSMISSEN of European Commission: “Why is it impossible to give a time interval and probability for the occurrence of next pandemic, and what are the main factors to make this possible?”

FERGUSON: “There is a 3 percent chance per year this will happen. But that’s simplistic. However, what’s the probability of a severe pandemic? There we cannot provide an answer: we don’t have the scientific knowledge yet.

“Avian viruses have been with us for many years. Even though H5N1 is much more recognizable than 10 years ago, we don’t have evidence that a pandemic is more probable now than 20 years ago. But if it does break out, its severity will be the problem. The risk of its severity has gone up. This has implications for policy planning. If we were sure of its imminence, you could plan. Much harder is when there is a smaller risk and you have to persuade authorities to make preparations.”

OSTERHAUS “We haven’t seen a pandemic during the last 30-to-40 years but that doesn’t mean it’s more likely – or less. In my own country, the Netherlands, there is fear of flooding. We will spend EUR 1.5 billion each year for the next 50 years to guard against this, even if the likelihood of a major flood is one in 10,000. Let us remember that the risk of an outbreak of pandemic is much higher than that.”

MONTO: “The most receptive audiences for pre-pandemic planning are in California, due to the risk of earthquakes they have experienced. This makes them open to pandemic planning. Indeed, the attitude there is: you may be preparing for nothing, but it’s better to be ready when it does strike.”

### *Question*

David REDDY: “The low percentage threat of a pandemic sets us up for a fall. We often underestimate the effort that the developing world has done to eliminate it from their bird stocks. Yet H5N1 is currently very spread out geographically and is very persistent: is this a factor?”

OSTERHAUS: “Given that HP H5N1 has persisted for such a long time and has created 10 sub-clades is absolutely unprecedented. The fact that H9 has spread even more widely is also unprecedented. This probably has to do with the way we manage our bird stocks, and the migratory element. From a veterinary point of view, we have to be careful regarding the huge production scale of poultry and poultry products.”

### *Question*

Hans HOUWELING: “Is it realistic to talk about pre-pandemic vaccination for England? Also: isn’t the safety record of pre-pandemic vaccines limited so far?”

VAN-TAM: “I agree that we just don’t know what the next pandemic will be. There are H 5, 7, 9 and 2, and it’s a brave person who would bet against H5 with certainty.”

*Question*

HOUWELING: “And the safety record?”

VAN-TAM: “Regarding the development of H5N1 vaccines: there is no vast experience with safety. But at least one of the adjuvants has been used in Europe for probably a decade. What is equally important is that if we give a novel vaccine to a population as large as that of Europe, it will generate a certain public signal. If we need to deploy a vaccine on that scale without clinical experience, we’ll need to monitor it carefully and to deal with the scare stories that will inevitably emerge in the press.”

*Question*

HOUWELING: “What would the uptake be of such a pre-pandemic vaccine?”

VAN-TAM: “That depends on when you give it and how frightened the population would be at the time you administered it.”

OSTERHAUS: “When we had the first case of human H5N1 at Europe’s doorstep, the remarks of the European Commission sparked a huge run on seasonal vaccines. Result: stocks in the Netherlands were sold out in one week compared to the usual period of six-to-seven weeks.”

Luc HESSEL of Sanofi Pasteur added: “Thanks to research we’re in a position to move from science to policy. This makes possible pre-pandemic strategies. But you need specific guidelines in terms of regulation. EMEA [the European Medicines Agency] has put forward a set of guidelines for pre-pandemic and TPP [target product profile] vaccines. For a start, we are talking about using avian flu vaccines in humans. We are inoculating the vaccine to prevent something that is not a human disease yet.”

*Question*

Karl EKDAHL of Stockholm-based European Centre for Disease Prevention and Control “One of the dangers is the risk of side effects that we don’t see in time. If so, this could be very detrimental to public trust. Thus, we need to have systems in place for early detection of side effects, no?”

OSTERHAUS: “You will only find these in the post-marketing deployment phase. You can only learn about it by doing it.”

MONTO: “What you are talking about is enhanced surveillance with early use. In the rush to get vaccine used in an emergency, the signal will not be easily recognized.”

*Question*

Itamar GROTO: “I have a question about masks. The official position is that there is not much evidence about their efficacy. But let’s assume the opposite: shouldn’t we have some kind of stockpiling strategy on masks?”

FERGUSON: On the evidence side, there is little to point to. The interesting aspect of a recent study we’ve done in Australia about the use of masks in the home suggests there has been little effect. The lesson for policy is that people will wear them during pre-pandemic stages, but the costs are staggering if everyone is to have one. My own view is: we need more sociological research before we can make any recommendations.”

OSTERHAUS: “The use of masks in the Netherlands during avian outbreaks was the following: we found in general it had a negative effect. Poultry workers may use them while cleaning out infected poultry, but then they wipe their faces, which is probably counter-productive.”

VAN-TAM: “The evidence is insufficient to determine what is the most effective transmission model and thus the impact on protection offered by masks. Do they prevent droplet transmission or just protect the face against direct contact?”

OSTERHAUS: “Many wore masks during the SARS episode in Hong Kong, but social distancing fell off as did the use of public transport. The isolating effect of masks will be difficult to assess.”

FERGUSON: “Even if a mask offers 30-40 percent protection, that’s good. But the problem is: how do you ensure a high level of compliance among the population?”

### **Workshop Conclusion**

OSTERHAUS (to audience): “We’re not as empty-handed as we were decades ago. Policy-makers have a range of options: medical and non-medical intervention, surveillance, antiviral stockpiling, and the stockpiling of vaccines that might be used at the beginning or during Stage Four of a pandemic.

“I would like to ask you: what do you need? Is there anyway we can help you further? We’ve offered a number of ideas on pre-pandemic planning, but is there more we could do?”

In the meantime, he said, ESWI will write up the conclusions of today’s discussion “to see where we have a consensus for further debate and follow-on action. Thank you all for attending our workshop.”

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