

Public Accounts Committee

Oral evidence: Tamiflu Recall, HC 677

Monday 20 October 2014

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Members present: Margaret Hodge (Chair); Mr Richard Bacon, Chris Heaton-Harris, Meg Hillier, Mr Stewart Jackson, Austin Mitchell, John Pugh

Gabrielle Cohen, Assistant Auditor General, National Audit Office, Laura Brackwell, Director, National Audit Office, Sue Higgins, Executive Leader, Local Services, National Audit Office, and Marius Gallaher, Alternate Treasury Officer of Accounts, were in attendance.

Witnesses: Professor Dame Sally Davies DBE FRS, Chief Medical Officer, Department of Health; Sir Andrew Dillon, Chief Executive, National Institute for Health and Care Excellence; Richard Douglas, Director General of Finance and NHS, Department of Health; Dr Fiona Godlee, Editor-in-Chief, British Medical Journal; Professor Carl Heneghan MRCGP, Director, Centre for Evidence-Based Medicine, University of Oxford; and Dr Ian Hudson, Chief Executive, Medicines and Healthcare Products Regulatory Agency gave evidence.

Chair: Thank you for waiting. I don't know what time you were told the hearing would start, but we had a vote, which probably made us a bit later than we should have been. Would it be sensible for everyone to introduce where they are from?

Mr Bacon: Yes.

Q1 Chair: Richard is going to lead for us. Sir Andrew, do you want to say which bit of the world you come from and why you are here?

Sir Andrew Dillon: I am Andrew Dillon, chief executive of NICE.

Dr Hudson: I am Ian Hudson, chief executive of the MHRA.

Professor Dame Sally Davies: I am Sally Davies, the chief medical officer.

Richard Douglas: I am Richard Douglas, director general of finance and NHS at the Department of Health.

Professor Heneghan: I am Carl Heneghan, professor of evidence-based medicine at the university of Oxford and a GP in Oxford.

Dr Godlee: I am Fiona Godlee, editor-in-chief of the *BMJ*.

Q2 Mr Bacon: Thank you all very much.

I will start with you, Dr Godlee. I originally got interested in this subject because of a letter you wrote to NICE some time ago—I think it was the year before last. Because of your concerns about NICE approval for Tamiflu, you asked it to withdraw its approval until it had received and reviewed the full clinical trial data. Subsequent to that letter, which was drawn to my attention, the NAO did this Report. Could you remind the Committee why you wrote that letter and what then happened?

Dr Godlee: Yes. I will try to be brief, as Carl Heneghan perhaps has more personal involvement in the story. The Cochrane Collaboration was asked by the NIHR in the UK to look again at the data on Tamiflu. When it did so, it became aware that the trial basis on which Tamiflu had been considered effective involved 10 trials, all of which were industry-funded and only two of which had ever been published in peer-reviewed journals. The collaboration began to seek access to the raw data from those eight to 10 trials, in the process of which it became clear that those data were not held by the investigators, but by the industry sponsor.

Q3 Mr Bacon: Do you mean that they were not publicly available?

Dr Godlee: They were not publicly available, nor were they in the possession of the principal investigators. They were held solely by the company that owns and manufactures Tamiflu—Roche. Over the course of some years, I got involved, through the *BMJ*, in trying to support the Cochrane Collaboration in gaining access to those data so that it could fulfil its promise to review the evidence on Tamiflu. The letter to NICE was really just one more effort to find what levers we had available to us to put pressure on Roche to make the data available to the Cochrane Collaboration. After a series of similar levers—the letter to NICE; the letter to John Bell, who is on the Roche committee and is the regius professor in Oxford; and those to other influential people who might be able to pull strings or to use influence to get the data made available—eventually Roche made the data available to Cochrane. Carl Heneghan can tell you the conclusions of that analysis.

Q4 Mr Bacon: I will come to Professor Heneghan in just a moment.

Mr Douglas, when the NHS is procuring drugs, and particularly when it is buying stockpiles, it depends on assurances—that was highlighted by the NAO in its original Report. Paragraph 1 of that Report says: “Assurance to underpin the procurement of stockpiles comes from business cases, which should use the latest evidence on efficacy.” It goes on to say, in paragraph 2, that the business case for Tamiflu was approved—I am sorry, I have jumped ahead of myself. It is actually paragraph 3.24 of the Report, which says: “The business case was agreed within the Department by its Revenue and Investment Branch and Finance Director”—that is, by you. Moreover, the previous paragraph, paragraph 3.23, says: “Antivirals provided a net benefit across all scenarios used in the business case, when compared to scenarios with no antivirals. Benefits were calculated by estimating reductions in hospitalisation, complications and death rates due to the use of antiviral medicine and

assigning economic values to these benefits.” Presumably you were working on clinical advice, when you signed off the business case, that the relevant evidence on efficacy was available. Is that correct?

Richard Douglas: Yes.

Q5 Mr Bacon: Dr Hudson, you are now the chief executive of the MHRA. That’s right, isn’t it?

Dr Hudson: That is correct.

Q6 Mr Bacon: Was your predecessor Sir Kent Woods?

Dr Hudson: Yes, indeed.

Q7 Mr Bacon: Sir Kent Woods told us in the hearing last year: “I am confident that we had access to all the relevant data”. Was he wrong?

Dr Hudson: No, not at all.

Q8 Mr Bacon: You think that he had all the relevant data available, do you?

Dr Hudson: The regulators are able to get all the relevant data from companies. It is a requirement on companies to submit all data relevant to an application. I should stress that Tamiflu has been authorised through the centralised procedure through the European Medicines Agency, so it will have gone through the EMA and the CHMP, in a commission licence. CHMP and EMA have reviewed the data on a number of occasions and have been satisfied that they have the totality of the data.

Q9 Mr Bacon: So you remain confident that the MHRA had access to all the relevant data, as Sir Kent told us last year?

Dr Hudson: The regulatory system? Yes, I am confident.

Q10 Mr Bacon: Well, he actually said: “I am confident that we had access to all the relevant data”. He was speaking in his capacity as chief executive of the MHRA.

Dr Hudson: Yes, indeed.

Q11 Mr Bacon: Professor Heneghan, we heard from Dr Godlee a moment ago that there was some difficulty in getting access to all the data, but that it eventually emerged and you were then able to assess it. Can you tell us what happened—the process of it—and what your conclusions were?

Professor Heneghan: So as to be clear, if we go back to the story, in 2005, when the original reviews came out, which were important and illustrated and reported a two-thirds reduction in pneumonia, a Japanese doctor put a comment in to one of those reviews saying, “You have made a mistake because eight of the 10 trials you have used have never been published—including the largest treatment trial ever, to date, M76001, which remains unpublished. You incorporated that into your results based on the findings of summaries of four employees of Roche, who published that in one study, which was a shortened narrative. Those trials have never been made available.” We then set out—

Q12 Mr Bacon: Can I just stop you? If it were correct that there was a two-thirds reduction in pneumonia, that would be quite impressive, would it?

Professor Heneghan: Yes. That is a reasonable assertion for putting any drug into use. That type of reduction is an incredibly important reduction to use in clinical practice, and the sort of large treatment effect that you would want to be in a position to purchase. I think you can correctly say that, if you felt that was the full evidence base. The people who were involved in that original adult review, including Tom Jefferson, have gone on public record to say that they were part of the problem and made those mistakes, because they used that evidence to put forward and then publish that in the public domain in the Cochrane review.

It was only when the Japanese doctor pointed out that eight of the 10 trials were not published—large-ish treatment trials—that we decided in 2009 to pool our resources between adult and children trials to try and obtain what are called the clinical study reports. In that process, we went to the US FDA, to NICE, to the MHRA, to the European Medicines Agency and to Japanese regulators to see what they had got. They gave us partial study reports and an incomplete part of the evidence base that they had looked at and had in their acquisition.

We then wrote to the companies and asked for the data and the trial authors. Some of the trial authors said they had never seen the data, never participated in the trials and had not got access to the data, and that we should go to the company. More or less everybody who participated in every single study had no access to the data. We actually then went to access the data through Roche, who stonewalled us, and we went for the other competitor, GSK, at the same time.

It was at this point that we then had to start involving the *BMJ*, and we involved media people and started writing, including to Channel 4 News, to try and put pressure on to the company to provide the data. It was at this point, as we moved forward, that we received funding from the National Institute for Health Research to carry on, because it is a large data set. That was a four-year mission to make the data available, and I am pleased to say that the data are now fully in the public domain on a repository called Dryad that anybody can access, and it is about 170,000 pages of all the clinical study reports of the randomised controlled trials that exist.

Q13 Mr Bacon: And if you were, on the basis of the data now being fully available, to draw conclusions about the efficacy of Tamiflu for not simply preventing people from getting a cold, but preventing people from getting complications such as pneumonia and preventing people from dying as a result of pandemic flu, what would be your conclusions?

Professor Heneghan: If I was to draw an analogy between 1999-2000, when it first was licensed, and where we are now, it still has the same symptomatic benefit—about a 20-hour reduction in symptoms of headache and temperature.

Q14 Chair: 20 hours.

Professor Heneghan: 20 hours' reduction—about equivalent, if you want to say it, to taking a paracetamol. You may take some other form—

Q15 Mr Bacon: Lemsip has paracetamol in it, hasn't it?

Professor Heneghan: Yes. You may want to argue that, in terms of the science, we are interested in temperature, because you could argue that, in terms of temperature, it is good for healing, but let us leave that. That effect has been consistent throughout.

Q16 Mr Bacon: That is widely agreed.

Professor Heneghan: Yes. However, there is no effect on symptoms in asthmatic children, although there is in healthy children, so for those children with more complications, there are no effects now. That is probably because the complicated children—more complex, like asthmatic—are already receiving symptomatic treatments that will have an effect, such as steroids or bronchodilators. There is no effect on hospitalisation.

There is an absolute benefit of a 1% reduction in what we call self-reported pneumonia. That means that what was actually collected on the case report forms was, "Does the person think they have pneumonia? Yes/No." None of the trials was set up actually to investigate the complication in pneumonia. When we looked at any single studies that used verifiable pneumonia—that means by an X-ray—there is no effect whatsoever. That is incredibly important in how you set up clinical trials—you want an objective measure. You can ask me about clinical practice and somebody coming to say, "I see patients all the time who will say they have pneumonia." That an effect of the symptomatic reduction—that is very clear. So, with that, there is no effect on pneumonia. For children and prophylaxis, there is no effect.

Q17 Mr Bacon: Can you just explain to the Committee what prophylaxis is?

Professor Heneghan: That means if you give it when you don't have flu. So if you have given it before—to prevent you getting flu—there is no effect on pneumonia reduction. It increases nausea and vomiting, which is consistent with what was reported in 1999-2000 in the review, so we know that increase: about one in 20 will have more nausea and vomiting. More importantly, in the prophylactic studies, there is no reduction in transmission.

Q18 Chair: So actually it makes people worse, rather than better.

Professor Heneghan: One of the key issues to stockpile a drug is to reduce the transmission of influenza. If I give the room the treatment, hopefully what will happen is the number of people

getting the infection will go down. What it does is, just like with the symptoms, there will be a small reduction, with some people who report lesser symptoms if you give it to everybody prophylactically. Importantly, it does not reduce transmission. Then again, and this is the other important finding, no serious adverse events were reported in the original reviews and that has been replicated by other bodies. We found serious adverse events and, for every 100 people, one person will have serious psychiatric adverse effects, and it is about the same for renal complications, because the drug is renally excreted—so the renal effects are serious in their nature, and that was not known before.

Q19 Mr Bacon: The kidney effects.

Professor Heneghan: Yes. What happens if you excrete drugs through your kidneys is that, if you have got any renal complications and particularly if you are having a problem, it can make your excretion slightly worse, to the point where it can make the imbalance in your body give you renal complications, which you do not want. Many drugs actually do that—non-steroidal anti-inflammatories have that potential.

They are all the additional complications that we now know about. So in effect, what we have said is, in the context of having all the clinical study reports, that we can produce an accurate estimate of the benefits, with objective measures, and an accurate estimate of the harms.

Q20 Mr Bacon: Which is presumably what you would want to do in any event before deciding. It is the assessment of the benefits versus the assessment of any potential harms that underpins the business case, isn't it?

Professor Heneghan: Correct. In effect, additional to that, you want to know two aspects equally. First, what does it do in healthy individuals? In healthy individuals, we know that it does not actually do anything in terms of the benefits-harms ratio. The second question you would want to ask is about high-risk individuals. What is surprising is that there is still no study within a hospital population of this treatment; it is all in the community—in primary care. Most of the evidence that comes from hospital derives from observational data. There has been a lot of criticism about the lack of randomised control data compared with observational data in hospital.

I will just give you one of the interesting issues. When we published our original review in 2005, with all the poor data and all the problems, no one had a problem saying, "That randomised trial evidence is okay." With what we are publishing now, it seems to be inadequate, and it does not quite fit the question that we want to ask. It does not answer, in high-risk people admitted to hospital, whether we should use this treatment, because there is no single trial for that.

I want to finish on one important point. Peter Doshi wrote an article on the story behind the review, and it is very important to understand this. In America, they took more evidence than we did, because we have seen what they looked at. Roche had to set up different websites for America and Europe, because in America it said: "Treatment with Tamiflu has not been proven to have a positive impact on" asthma, emphysema, other chronic lower respiratory diseases, pneumonia, other respiratory diseases, pneumonitis, and influenza-related death. That is backed up by the US FDA: "Serious bacterial infections may begin with influenza...Tamiflu has not been shown to prevent such complications." In Europe, however, we have the website called roche.com saying, based on

the Kaiser review: “Tamiflu delivers...67% reduction in secondary complications such as bronchitis, pneumonia and sinusitis in otherwise healthy individuals”.

Q21 Mr Bacon: Is there something different about the human beings in North America due to which different results would be scientifically likely?

Professor Heneghan: I will not answer that; maybe the Americans would like to answer that. What is different is that the US FDA is a public body, which produces reports and makes them all transparently available—they are on the website and they have to be seen when it puts its judgment. Its judgment has been on that website for some time. It looked at more of the study reports and did more of an in-depth job than we did in Europe.

Q22 Mr Bacon: I want to come on to what the chief medical officer and others have to say in response, but first, just so we are clear, am I right in thinking that the reason why we would spend hundreds of millions of pounds on stockpiling a particular drug is so that, if there were the risk of pandemic flu, we could give it to people as a preventive measure? That is to reduce the chances that they would—

Professor Heneghan: There are two reasons why you would have a treatment in a pandemic. First, because of its effects on complications, which are important if found to be true—if that was true, you would want to make that treatment widely available. That is important. Secondly, you want it to be able to prevent the transmission of the disease while, first, you get your act together and, secondly, try and get a vaccine out to all the population. But let me tell you, even if it did have an effect on transmission and you decided to go down that route, you would have to make the treatment available to 80% of the population for eight weeks. They would have to adhere to the treatment, and then at the end of eight weeks, you would need to have the vaccine available. So the modelling for these strategies are based on incoherent practices that are not pragmatic and are unfeasible to deliver.

It is very interesting; you can look at all sorts. There has been an analysis in Oxford—I have a paper here—that looked at the waste water to see how much was thrown away in the pandemic: 50% of the drug ended up in our sewers.

Q23 Mr Bacon: It does not sound like a good use of public money.

I will come to Sally Davies in a moment, but you mentioned a figure of 1% in relation to serious psychiatric episodes. Let us say you gave it to a million healthy people. You mentioned that it does not help with the complications of pneumonia or with transmission, and that there is a risk of nausea and vomiting, and potential risks with kidney problems and serious psychiatric episodes. How many otherwise healthy people might suffer from these conditions?

Professor Heneghan: Well, you do the maths. It starts to scale up—that is the key. If you have a treatment that is beneficial, it will outweigh the 10,000 people who are harmed. Now you ask yourself the question: why in Japan does the drug have a black-box warning in adolescents? Because some sub-groups, like adolescents, have had serious complications with hallucinations and psychiatric complications, and some people have gone on to commit suicide. The evidence behind

that means that in certain groups, you would start to be concerned, so when you know that, you would want to be clear that the benefits outweigh the harms.

Q24 Mr Bacon: I was about to say you might still want to do it if you thought that the benefits were significant.

Professor Heneghan: And all drugs will have adverse effects. That is the key about the transparency issue. To understand the benefits and the harms, you need to make all the evidence available and then let individual clinicians and patients make judgments. We know that if you use the published summary data, about 80% of the adverse effects will not be put in the published summaries in the small four or five-page articles that are in journals.

Q25 Mr Bacon: Professor Davies, do you think the Cochrane Collaboration's conclusions are fair on the basis of having obtained all the evidence?

Professor Dame Sally Davies: It is a systematic review done for seasonal flu that underestimates the results because they are not, as they would be for licensing, proven to have flu and they are healthy people, so it is as good as it stands—otherwise we would not have funded it. But we are talking about something different here; we are talking about pandemic flu, which is top of the Government's risk register. We have to have defence in depth, and I think that what you are interested in is whether there is a read across. Clearly, it is a bit like lemons and limes. They are both citrus fruits and you can use them for the same recipes, but they are different. The big difference in a pandemic is that there is no background immunity, and we will have no vaccines for a minimum of six months.

Meanwhile, if it were like the 1918 one, when 80 million to 100 million people died, we can overwhelm our health service. We could find that there are not people to look after our children, our economy could collapse, and we could have real problems, so we have to plan for what is known as the reasonable worst case, which is not as bad as it could be.

I can take you through our planning, our modelling and who it was done by, but there are rather optimistic assumptions about the impact that coverage of the stockpile would have, and the precise division of deaths between those at risk and the general population actually determines the cost-effectiveness.

Q26 Mr Bacon: Just a minute. You mentioned the modelling. Paragraph 3.23 of the NAO's original Report talks about the work having been done by the Scientific Pandemic Influenza Advisory Committee. It advised that an assumption of a 40% to 50% reduction in both hospitalisations and deaths should be used in the modelling for the paper. We have heard from Professor Heneghan that, actually, there is no effect on hospitalisations or complications, so is it not fair to say that the business case was flawed because it did not look at all the evidence?

Professor Dame Sally Davies: No, I don't think it was flawed. Again, I'd like to explore the concept of evidence-based medicine. We start with randomised controlled trials, we then look at all our evidence, and then we look at it in the context of the patient. For evidence-based policy, we start with randomised controlled trials. Unfortunately, they are not in a pandemic, and our ethics

committee at the time did not feel it was ethical to do a randomised controlled trial, as I understand it. Then we have to look at other evidence.

We now have more evidence, collected by Muthuri—observational evidence, but real individual patient data, meta-analysed in 29,234 patients from 78 studies—and it showed that during the pandemic, mortality dropped by half when it was given within 48 hours of clinical symptoms and by a fifth if it was given later. If you start to drop mortality like that, you are taking pressure off the health service.

Q27 Mr Bacon: You say when “it” was given. Are you referring to Tamiflu?

Professor Dame Sally Davies: Yes. I would also like to highlight the data from Japan, where they used it very generously—shall I say?—in pregnancy. I am trying to find the table from Public Health England.

Q28 Mr Bacon: While you find it, let me ask Professor Heneghan to respond, because I think he knows something about evidence-based medicine—he is the director of the centre for evidence-based medicine at Oxford. Professor Heneghan, I want to come to the broader issue of the availability of data and our recommendation from last time, with which the Government disagreed. Can you respond briefly to what Professor Davies said?

Professor Heneghan: Yes. What Professor Davies is saying is that in the hierarchy of evidence, you start with the highest level of evidence, which is systematic reviews. Then you go down to randomised trials and, below that, observational data, which is what you observe in practice.

The problem with observational data is that it is subject to confounding. We have known for 50 or 60 years that, in effect, when you observe what has happened, what you see is confounding by indication. People with worse prognoses do not receive the treatment as prescribed. In effect, if you were seriously unwell and came to see me, and I thought you had pneumonia and needed to be sent to hospital, I would not be messing about with Tamiflu based on the clinical trial evidence. I would ring the surgeon, and we would think about X-rays, antibiotics and appropriate treatment. However, milder, more well people tend to be treated, and then some of them may be admitted. When you come to observe that, hey ho, what you see is a very large reduction in mortality, but so many biases underpin that effect that you would not want to use it to say, “This is how we are going to estimate our treatment effect.”

You could argue that within the confines of a pandemic, you did not have the time to run a trial. That is fair enough but, generally, if you see a mortality reduction in a pandemic, you should ask, “What’s the mechanism? Is that caused by less pneumonia?” You should still see some mechanisms within the clinical trials in seasonal flu that would underpin the mortality reduction.

Q29 Mr Bacon: And in this case, you know there is no mechanism.

Professor Heneghan: That is the issue. You do not suddenly say with lower-risk people, as with heart disease, “We don’t see any deaths.” It is a question of power and of size. But you would still say, “They have less angina, but we don’t see the mortality, because we cannot do enough trial.”

Let us just reiterate: when the evidence in the trials was showing benefit, it was okay to come to a judgment on it. When the evidence does not show a benefit, we say, “Okay, let’s look at some observational data.” Observational data does have uses, and it is important, but many people in this room know that it is subject to such bias that you would not want to use it to establish treatment effect.

Q30 Mr Bacon: We have to move on, because we don’t have a lot of time. One thing that we heard last time was that trials with positive results are about twice as likely to be published as trials with negative results, which sounds like a pretty good argument for having access to the entire evidence base rather than some of it.

I want to get on to the question of the Government’s disagreement with our first recommendation last time, which was that “the full methods and results are available to doctors and researchers for all trials on all uses of all treatments currently being prescribed”. The Government said that that would not be feasible. Can you say—Professor Davies, Sir Andrew or Dr Hudson, I do not mind who—why that is not feasible?

Dr Hudson: First of all, perhaps I could update the Committee on the quite significant developments in terms of registration and publication of trials—

Q31 Mr Bacon: I would really like you to answer my question, which is about why you think it would not be feasible. If you want to update us at length, you can do that in a note, but we are quite short of time. The Government said, “It would not be feasible for the full methods and results to be made available for all trials and uses on currently prescribed treatments”. Why wouldn’t it be feasible?

Dr Hudson: I think a lot of progress has been made, and we have got to start somewhere. All trials have been registered on the EudraCT database since 2003, and this was made public in 2011. Since July this year, the Commission has asked all sponsors of trials to populate it with summary results. Similarly, we are making progress in getting publication of the full-study reports. There are different levels of data: there is summary data—

Mr Bacon: Yes, clinical study reports are much more detailed.

Dr Hudson: Indeed, but—

Q32 Mr Bacon: You are telling me what has been done. My question is about the Government’s stated disagreement with the Committee’s recommendation. It said, “It would not be feasible for the full methods and results to be made available for all trials and uses on currently prescribed treatments”. I am asking: why does the Government think that it would not be feasible?

Dr Hudson: It is a question of starting somewhere and making progress to try to get as much information out there as possible, particularly prospectively. So, for example, in terms of registration and results, the EudraCT database, which is the database for clinical trials in Europe, has been populated since 2004.

Q33 Mr Bacon: You are basically saying, “It’s a big task.” But I am really asking you a different question, which is why the Government believes it would not be feasible. That is what it said. I want to understand the Government’s thinking. That is the Government’s opinion, not mine. I am just asking you to explain it.

Dr Hudson: There is a question of what should be prospectively put out and there is a question of what is available on request—

Q34 Mr Bacon: Let’s deal with that prospective point very quickly now. Is it the Government’s position—I understand it to be this, but correct me if I am wrong—that, from now on, the full methods and results should be made available prospectively for all trials and all treatments?

Dr Hudson: The Government’s position has been very much to support the transparency agenda. I think in the response before it made reference to the clinical trials regulation that was coming forward and also the EMA transparency policy. Both of those have now progressed significantly, such that, with the clinical trials regulation, which was agreed and published in the *Official Journal* in June, when it comes into force in two years’ time, there will be a requirement for summaries to be published within a year of the completion of the trial. Secondly—

Q35 Mr Bacon: Summaries of all methods for all uses, for all treatments?

Dr Hudson: On the EudraCT database already there is a description of the trial, including elements of the protocol: the design of the trial is there and in the public domain already. I am now talking about the results of the trial—a summary of the trial at the end of the study. In addition to that, for studies that support a market authorisation, there will be a requirement that the full-study reports—with appropriate removals if there is patient identifier information or particularly commercially confidential information—should be published at the time of the decision.

Q36 Mr Bacon: So, if I may summarise your summary, you are basically saying that the Government is in favour of full transparency going forward, prospectively—is that correct?

Dr Hudson: That is correct, yes.

Q37 Mr Bacon: Okay, good. Now, back to my original question: why is it not feasible to do that for all the currently prescribed treatments that are out there and being used?

Dr Hudson: Retrospectively, data is available. First of all, there are public assessment reports that are issued, and have been issued since 2005—

Q38 Mr Bacon: I hate to labour this point, but I am not asking you to list the different types of data; I am asking you to explain why it is not feasible to make it all available.

Dr Hudson: And secondly, information is available on request. We operate under freedom of information rules, so if someone comes to us and asks for clinical data—

Q39 Mr Bacon: Again, you are answering a different question. The Government's view is that, "It would not be feasible for the full methods and results to be made available for all trials and uses on currently prescribed treatments", and I am trying to understand why it is not feasible.

Dr Hudson: First, the policy must be done in conjunction with our colleagues in the rest of Europe. Secondly, we have got to start somewhere and be clear about the policy.

Q40 Mr Bacon: Trying to climb Everest is a very big task, but just because it is a big task people do not say, "It's not feasible to climb Everest." We are not talking about the scale of the task. I understand that if one were to do this for all currently prescribed treatments—all the drugs that are used—it would be a very big task; it would be an Everest. But we don't say, "Ergo, you can't climb Everest"; we assess the scale of the task and set about dealing with it. We get the relevant equipment and go off to climb Everest. I have been listening to you for a while, and I still don't understand why the Government's position is that it is not feasible to make available the full methods and results.

Dr Hudson: As you say, it would be a huge task, with 15,000 medicines on the UK market, and we must look at what it is sensible and rational to do prospectively, and what can be done retrospectively.

Q41 Mr Bacon: The information is held by the people who did the research. Correct?

Dr Hudson: Yes, indeed.

Q42 Mr Bacon: So it would not be an enormous burden on the Government if you said, "Make it available." It would be a burden, in so far as it is a burden, severally on the bodies, drugs companies and institutes of research that did the work. Isn't that right?

Dr Hudson: Well, it has got to be practical and feasible, and it has got to be—

Q43 Mr Bacon: Sorry, I am asking you where the burden, to the extent that it is a burden, of making this information available would sit. Where would the effort have to come from? Would it be from you or from the people who hold the data and who would be obliged to make it available?

Dr Hudson: It could be both parties, because we would hold the data as well, in terms of supporting the licence. It is a question of what can be done prospectively and what can be done retrospectively, in relation to what other colleagues across Europe and beyond are doing.

Q44 Mr Bacon: Professor Heneghan, I understand that there will be issues around the scale of the task. Plainly, getting the information for all trials and uses on currently prescribed treatments is a big task, as we heard from Dr Hudson. I would be interested in your views on whether it is feasible, notwithstanding the fact that it is a big task. Secondly, if we have to start somewhere, as Dr Hudson keeps saying, is it not worthwhile to identify the drugs that are currently prescribed about whose efficacy there are similar concerns to those about Tamiflu, because the full evidence base was

not available when they were originally approved? Would one way of doing it be to work one's way through from the drugs that are of the most concern?

Professor Heneghan: When you say 11,000 conditions, or 8,000 drugs, you think it is insurmountable, but it is not if it is boiled down to clinical practice in a GP. My practice uses the 80:20 rule—we use about 80 drugs. I could take you to the out-of-hours and show you that all the drugs we use fit into one or two cabinets.

Q45 Mr Bacon: Did you say 80?

Professor Heneghan: Yes, 80 drugs. They are the most commonly utilised in primary care. We do not need to look at 5,000, because some of those drugs are used in single patients. If you go for the whole lot, it is insurmountable. The WHO has a call-out at the moment, because it is about to issue guidance on clinical trial registration. I put in an amendment and said that the WHO essential medicines list covers about 300 medicines. It is not just important for us; globally, it is a similar issue. We are talking about the 300 most used medications.

The second thing, which is a profoundly important issue that we could change, is that we are making this data available not only for us but for future generations that may come back and say, "We would like to look at those trials, which were done in untreated populations." We may never be able to do some of these trials again. I think you could create a sensible list. The first thing is to create an inventory of what we have and do not have; that is helpful. If we knew that, that would be the first step. I think it is feasible. It will take time, but somebody has got to make a decision to go back, look at the common treatments used in practice and see what is available to us.

Your second question was, are we doing that? This is not only about harm, but about benefit and implementation. Clinicians are aware of the problems of having a partial evidence base, so they tend to respond by getting the guidance and doing exactly the opposite. They hold back and say, "I'm not going to use this treatment, because we've been down this route before. We don't think we've got all the available evidence yet, and we're going to wait." There are examples; the new oral anticoagulants are a bit like that—all the manufacturing trials are done, issues are starting to emerge about the trials, and there have been lawsuits in America. It could be a great drug, but the problem is that if you do not provide an impartial evidence base and make it fully available, not everybody can come to the conclusion they need. There are certainly drugs—and devices, but mainly drugs—out there for which you could say, "We think these have issues, for these reasons".

Q46 Mr Bacon: These are currently prescribed drugs?

Professor Heneghan: Yes. In January 2016 the European Medicines Agency is going to make the clinical study reports available going forward. Going back, we have asked for some, and people are going to the European Medicines Agency to make freedom of information requests. I have a freedom of information request in now for a class of drug called direct thrombin inhibitors, because we want to make the evidence available to understand how much benefit there is.

Q47 Mr Bacon: Could you just repeat that? What was the class of drug called?

Professor Heneghan: Direct thrombin inhibitors, otherwise referred to as new oral anticoagulants—NOACs. They are on the market to replace warfarin, in effect, because they do not have monitoring. However, concerns have been expressed about the evidence base. Again, it is about mopping up the evidence base. If we make all the data transparently available, we will be able to come to a better decision and understand the ratio of the benefits to the harms. That is all this is about. Without that, I am now clear, you cannot do that from summary published papers in journals.

Mr Bacon: I would like to ask a question about stockpiles and future policy, but I would like to let some of colleagues come in now, if they wish.

Q48 Chair: I want to know how much money we spent on Tamiflu.

Mr Bacon: Well, it was £424 million originally, wasn't it?

Chair: How much?

Dr Godlee: £500 million, the first one.

Mr Bacon: There was an additional £49 million.

Q49 Chair: I could not work this out from Professor Davies. Are you now saying that it was a waste or that it was alright?

Professor Dame Sally Davies: I would spend it again.

Q50 Chair: On Tamiflu?

Professor Dame Sally Davies: Yes. This is seasonal flu, and the observational data is strong. I prefer RCT data, but we will not have that in a pandemic. Let me be quite clear: it is supported by the experts, as shown by—

Q51 Mr Bacon: Are you saying that Professor Heneghan is not an expert?

Professor Dame Sally Davies: Not in flu.

Q52 Mr Bacon: I see. Keep going—it is supported by the experts.

Professor Dame Sally Davies: Who do understand flu and were working with patients at that time, and by the modellers. I can go through the modelling for you, but I do not regret having it. It was a mild pandemic; we were very lucky. We were worried that we might get H5N1, which had a mortality rate of 40%. At the moment H7N9, which has a similar mortality rate, is in China in birds and might come here. Meanwhile, there were studies on H5N1 in Asia that showed that it did reduce the mortality. But it will all be reviewed, because the Academy of Medical Sciences and the Wellcome Trust are going to do an independent scientific review.

Q53 Chair: Can I just ask Sir Andrew, who hasn't spoken—would you spend the money again?

Sir Andrew Dillon: Yes, I think it was the right judgment. However, it is worth making the distinction between the circumstances in which NICE issues its guidance for ordinary circumstances when flu is circulating in the population, and the very different—almost completely different—circumstances in which the country is facing a catastrophe. In those circumstances, there is a different frame of reference to exercise the judgment. Although it is the same underpinning data, the nature of the judgment you exercise in circumstances in which you are facing a catastrophic pandemic is quite different from the circumstances in which you—

Q54 Mr Bacon: Given that we know it does not reduce transmission and that it has no effect on pneumonia—it might help a bit if you have a headache, reduce flu-like symptoms or a cold, but it doesn't help with pneumonia or reducing transmission—why is it different?

Professor Dame Sally Davies: In the pandemic—

Mr Bacon: I beg your pardon, Professor Davies. I was asking Sir Andrew. He said that the data are the same, but none the less the conclusions you draw are different. I was asking why the conclusions you draw are different given that we know it does not help with—

Sir Andrew Dillon: With respect to Dame Sally, whose judgment is ultimately more important than mine in the context of a decision for national stockpiling—

Mr Bacon: I will happily come on to Professor Davies's answer as well, but I just wanted to know.

Sir Andrew Dillon: Sure. And bearing in mind that I was not involved in the process of making that decision for the Government, I am simply offering an opinion. It is different because the risk is different. In the case of the guidance that NICE produced, we made recommendations for a very small population of people during the ordinary circumstances when flu is circulating. It is a group of people who are already identified as being at risk. The advisory committee, looking at the data and considering the clinical plausibility of the effect of the drugs, makes a judgment in those circumstances. In circumstances where the country is facing a potentially catastrophic pandemic, the nature of the risk is fundamentally different and therefore the nature of the judgment is also fundamentally different.

Q55 Chris Heaton-Harris: Professor Davies, I have been fortunate enough to have been to the WHO's headquarters and have seen where they track these viruses as they spread. When in the timeline of this particular virus did we buy this Tamiflu?

Professor Dame Sally Davies: It started well before the pandemic. I think we started in '06-07, so the decision was taken quite a while ago. I can remember a very active debate in '07-08-ish around whether we had got the science right that Sir David King reviewed and agreed with. Clearly, as we have gone through, we have continued to maintain a stockpile, which has risen. It was raised at the beginning of the pandemic from 50% to 80%, and we have now worked it back down to 50%.

Dr Godlee: My understanding is that that decision was based on a systematic review of those 10 trials, so they were based on the very evidence that Professor Davies is now saying is not adequate to justify the criticisms that Carl Heneghan has made. We are blurring a whole host of things here. The only evidence available, which was publicly used as support for the decision, was the Kaiser systematic review, which was industry-funded by Roche, of 10 trials, only two of which had been published. That was the basis for the decision to stockpile the drug, as I understand it. It was based on seasonal flu.

Q56 Chair: Are you on common ground? Do you agree with that?

Professor Dame Sally Davies: No, there was quite a bit of other observational work that was not randomised. It was looked at by many scientists and reviewed by Sir David King, who agreed it. For seasonal flu, it has been reviewed by NICE. We now have much better data, which actually supports our use.

I found the Japanese data that I wanted to tell you about. It was very important that antivirals were given to 90% of pregnant women within 48 hours, with no deaths among pregnant women. We only got it into 60% and we had 12 deaths. Increasing observational evidence from the pandemic has been brought together and shows that there is an impact. Even the Cochrane review shows a saving of 16.8 hours for adults and 29 hours for children. Every day that you keep them out of hospital in the middle of a pandemic, you keep the system running.

Dr Godlee: To be fair, Professor Davies, you are merging various things. We are talking about symptom control compared with placebo, not with paracetamol, which may have been similar. We are not talking about keeping people out of hospital. The data on pregnant women refer to seriously ill women who were therefore a small proportion of people. It might be justified on that basis to create a pile of a certain amount of the drug, but not sufficient to medicalise the entire population—or whatever the figures would be. The amount that was bought was predicated on the idea that this would be given to healthy people, but we have no evidence, as far as I can tell, to support that decision. I think we must be extremely careful about why we are talking about large amounts of stockpiled drugs. Is it to give to healthy people or to the slightly fewer, but still large numbers, in a pandemic, people who might be seriously ill in hospital? They are very different groups of people.

Professor Dame Sally Davies: It is interesting that our advisers support this decision, as does the American CDC and the WHO. They have seen the recent review and have not changed their view. Public Health England, Japan, Germany, France and Netherlands all hold stockpiles and all believe that this is the right thing to do. It is WHO advice, CDC advice and Public Health England advice.

Q57 Chair: Very briefly, either Doctor Godlee or Professor Heneghan, would you please answer that point, so that we can get the two arguments clear in our minds?

Dr Godlee: About other people making the same decision?

Chair: Yes, or supporting the decision.

Dr Godlee: I am very impressed by the fact that the current evidence base is now available for public scrutiny. I would be interested to have them acknowledge that they have actually looked at those CSRs to the same depth.

Q58 Mr Bacon: CSRs being?

Dr Godlee: Clinical study reports. Have they looked at those CSRs to the same depth of detail as the Cochrane review?

Q59 Chair: Have they?

Professor Dame Sally Davies: That was seasonal flu. The observational study of more than 29,000 has been through the individual patient records.

Q60 Mr Bacon: Professor Heneghan.

Professor Heneghan: It is interesting. I am not an expert in flu. I am an expert in evidence-based medicine, because I have been interested in what it means when an individual comes to see me and we have an informed decision about what to do, based on the diagnosis and symptoms.

My job is to provide the patient with a complete and utter evidence base around the benefits and harms of the treatment. In doing that, in the period that this treatment has been available, I have yet to prescribe this treatment. That is the same for many of my colleagues. If you look at the prescription data, which I have done, you see that since 2011 the use of this treatment is fewer than 1,000 prescriptions per month. It has just not been used by clinicians on the ground.

Q61 Chair: Is that true?

Professor Dame Sally Davies: I would expect so. That is seasonal flu. What we do is allow GPs to use it if they feel they need to. It should be on a case-by-case basis. There can be an advantage and they need to decide. I keep explaining that a pandemic is a different matter.

Q62 Mr Bacon: You and Sir Andrew have said that before. I admit that I am a non-scientist, but it seems to me that if the drug does not work, it does not work. Sir Andrew said that we have to look at it differently because the risk is different, but the drug not working is not different. It continues not to work. It continues not to help with pneumonia; it continues not to help with transmission. Those things being true, they would continue to be true were there a pandemic, wouldn't they?

Sir Andrew Dillon: I don't agree that the drug does not work. If it didn't work, it would not be licensed.

Mr Bacon: Hang on, let's be quite specific. It does help reduce cold and flu-like symptoms. We know that and I think there is consensus about that.

Q63 Chair: By a day.

Professor Dame Sally Davies: It reduces mortality.

Q64 Mr Bacon: Can we have one person speaking at once? I am sorry but at the moment that is me. I am trying to ask Sir Andrew a question and get an answer to it. The issue is not whether it helps reduce flu-like symptoms and a cold. We know that it can do that. The issue is whether it reduces complications and whether it reduces transmission. We know, now that all the evidence is available, having been obtained by the Cochrane Collaboration and studied, that it does not have any effect with pneumonia or reduce transmission. My point, Sir Andrew, is that that remains the case whether you have something localised or a pandemic. It is still does not work, does it? Why would it be different just because, as you are describing, the risk is different? It still does not work.

Sir Andrew Dillon: It does work. It is a clinical judgment about the effect that the drug has, the balance of its benefits and harms, which have been carefully established by the regulatory agency, which is the place where NICE starts exercising a judgment. The question is whether it is the right thing to do to give the option for Carl Heneghan or any other doctor to consider with their patients using the treatment on the basis of the information that is available. Carl might, in individual circumstances, advise his patients that it is not worth it. He is entitled to do that; he is very well informed, as we have heard. The job that NICE has is to provide advice for the great majority of clinicians who are not in Carl's position to do the kind of work that he has done.

Q65 Mr Bacon: Hang on. You said it does work. I would like you to expand your previous sentence. You contradicted me and said it does work. Could you expand that sentence and say that it does work for—what? What does it work for?

Sir Andrew Dillon: It reduces the time to alleviation of symptoms, as we all agree.

Q66 Mr Bacon: So do paracetamol and Lemsip. You don't spend £500 million on Lemsip in cases of pandemic flu, do you? At least I hope you don't.

Sir Andrew Dillon: No. As far as I am concerned, on the basis of the evidence that is available, the treatment has an impact on patients' state of health. The question that we have to address, and that NICE has to address, is whether or not it is right to signal to clinicians and patients that it is worth them considering the use of that treatment in the very specific circumstances that we have, around people who are already at significant risk because they are part of the at-risk population.

Q67 Chair: Is it better than paracetamol?

Sir Andrew Dillon: It does what it is licensed to do.

Q68 Chair: Is it better than paracetamol?

Sir Andrew Dillon: Well, we haven't got a trial of paracetamol or Lemsip versus this treatment. We have got a whole array of clinical studies on which we have heard the results so it is not possible—

Q69 Chair: The only thing I would say to you is that this cost the taxpayer £500 million.

Professor Dame Sally Davies: It has. What I would ask you to remember is that the evidence base is broader than just randomised controlled trials. The Cochrane review is just randomised controlled trials and not even all of them are put in—some are still waiting to be put in—but it has ended up where it was a year ago so I expect it will end up about there.

There is much more evidence. The 29,200 or so patients who have been reviewed in individual patient data in the pandemic show that it significantly reduces mortality.

Q70 Chair: Better than paracetamol?

Professor Dame Sally Davies: Oh yes. Paracetamol does not reduce mortality in flu. I have mentioned the Japanese data, but there are other data out there. Where you get to is: do you believe that evidence-based medicine for an individual patient should be made only on randomised controlled trials? That is not how I was brought up. While randomised controlled trials hold a special place, there are other issues to bring into it. For policy, those randomised controlled trials inform, but massive observational studies are actually very powerful. For instance, we also know in this country that more than 1 million people received Tamiflu in the '09-10 pandemic. We know that we did not increase our rate of renal failure so we know that those severe problems that were being picked up are probably, in practice, rather rare. However, we know that nausea and vomiting occurred sufficiently in the pandemic to stop some people taking it.

Chair: I am going to go to Meg and then we will draw this to a close.

Q71 Meg Hillier: First, I want to clarify one point because something is going to be written down about this afterwards. Professor Davies, you talked about, and there has been a lot of discussion about, seasonal versus pandemic. With seasonal flu it is normal now for lots of patients to get vaccinated. Can anyone give a figure for what percentage of the vulnerable patients would be vaccinated now?

Professor Dame Sally Davies: From memory—we will send you a note—for the over 65s we get to about 75%, which is what we are aiming at. For the at-risk groups younger than that we get to around 50%, which is not very good. For children, which we are rolling out in pilots because there is a new “up the nose” one that has been recommended by JCVI, we got a take up in the pilot of 52.5%.

Q72 Meg Hillier: So those people, Professor Heneghan, clearly would not need Tamiflu prescribed because they would have the vaccines?

Professor Heneghan: The people in the randomised trials—

Q73 Meg Hillier: But when we were talking about not prescribing for flu, you would not prescribe it to a lot of people, but a lot wouldn't need it because they would get vaccinated. I am just thinking about that for balance, because I know that the vaccination programme has been very—

Professor Heneghan: The vaccination only covers though, and does not always cover the circulating strain.

Q74 Meg Hillier: But it covers at the time it is taken?

Professor Heneghan: Yes.

Meg Hillier: I should say for the record that I was a member of the Cabinet Committee where we discussed the flu pandemic. While we are hearing a lot of scientific discussion—I am not a scientist; at least not since my O-levels, which dates me—and there was serious and quite sober discussion when the pandemic's potential impact for Ministers from a range of Departments, and the public policy implications were explained to us. We were talking about wholesale school closures and all sorts of other mechanisms that would have severely disrupted British life. That was very much in the minds of the cohort of Ministers of which I was a part, particularly Ministers at the Department of Health. If you are sitting in any Professor Davies's hot seat, or any of those hot seats, that is obviously going to be a concern as well, so that is worth mentioning.

Q75 Chair: I'm going to allow Fiona Godlee to speak, and then I am going to have to draw this to a close. I am not 100% sure on where we take this.

Dr Godlee: In case there is any confusion, I think it is very important that people understand that we have trial evidence from about 300,000 seasonal flu patients, as Professor Davies said. My understanding of that evidence is that it shows that the drug largely does not work in seasonal flu. We do not have trials for pandemic flu, so we are having to resort to observational data, which are a much less good level of evidence. Those data may indicate some benefit in seriously ill patients—not in the healthy population—but they cannot be relied upon for evidence of benefit in the same way that clinical trials could be relied upon. The ethics of the situation during a pandemic mean that we must have a trial. If there is a pandemic, we must insist on a trial of Tamiflu or other, more modern antivirals, because not to do that would itself be unethical as we would be in the same position in years to come. On a general point, the current system is insufficiently transparent and insufficiently independent for the regulation and evaluation of drugs, and that has to change.

Q76 Chair: I hope that NICE vaguely agrees with that.

Sir Andrew Dillon: We are entirely committed to obtaining the best evidence we can and then exposing that evidence to the kind of pragmatic judgment informed by a broad range of stakeholders that goes beyond a simple interrogation of the data. Exercising judgment, either for a small population or for the whole country, in the face of a catastrophic pandemic is very different from a simple analysis.

Chair: Well, you have left us to exercise judgment, and I am not sure where we are going to do that. Thank you. That was a really interesting session, even if, for me, it ended up being a bit inconclusive.