UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

PEDIATRIC ADVISORY COMMITTEE

MEETING

TUESDAY, NOVEMBER 27, 2007

The meeting came to order at 8:00 a.m. in the Grand Ballroom of the Hilton Washington DC North, 620 Perry Parkway, Gaithersburg, Maryland. Marsha D. Rappley, M.D., Chairperson, presiding.

PRESENT:

MARSHA D. RAPPLEY, M.D., CHAIRPERSON
CARLOS PENA, PH.D., M.S., EXECUTIVE SECRETARY
DENNIS BIER, M.D., MEMBER
AVITAL CNAAN, PH.D., M.S., MEMBER
ROBERT S. DAUM, M.D., MEMBER
MICHAEL E. FANT, M.D., PH.D., MEMBER
MELISSA MARIA HUDSON, M.D., MEMBER
KEITH KOCIS, M.D., M.S., MEMBER
THOMAS NEWMAN, M.D., M.P.H., MEMBER
GEOFFREY L. ROSENTHAL, M.D., PH.D., MEMBER
ROBERT WARD, M.D., MEMBER
CAROLINE HALL, M.D., CONSULTANT
PETER L. HAVENS, M.D., M.S., CONSULTANT
DAVID W. KIMBERLIN, M.D., CONSULTANT
AMY J. CELENTO, , PATIENT REPRESENTATIVE
ELIZABETH GAROFALO, M.D., INDUSTRY REPRESENTATIVE
ELAINE VINING, CONSUMER REPRESENTATIVE
RICHARD L. GORMAN, M.D., PEDIATRIC HEALTH ORGANIZATION REPRESENTATIVE

T-A-B-L-E O-F C-O-N-T-E-N-T-S

P-R-O-C-E-E-D-I-N-G-S

8:06 p.m.

CHAIRPERSON RAPPLEY: Good morning. We'd like to get started if people would take their seats. Thank you. I would like to thank the members of the panel, those sitting at the table and those in the audience for attending the FDA meeting of the Pediatric Advisory Committee.

We have a very full agenda for three days and we are committed to staying on schedule and making efficient use of everyone's time. I'd like to thank members of the Pediatric Advisory Committee once again for your commitment to this important process. I would also like to thank the staff and the officers of the FDA for your tremendous effort in bringing these materials to us to discuss these medications over the next three days.

I'd also like to extend a special welcome to our guest from Japan, Dr. Nobuhiko Okabe. Thank you for joining us today and

we'll be hearing his remarks later this morning.

And, Carlos, I turn it over to you.

Sorry. I was premature. I'd like us to go around the table because we have some new members of the Committee and if we'd start -- let's see. Let's start down there and people would say their name and their institution. Thank you.

DR. BIER: I'm Dennis Bier from Baylor College of Medicine.

MS. CELENTO: Amy Celento, Patient Representative.

DR. CNAAN: Avital Cnaan, University of Pennsylvania and Children's Hospital, Philadelphia.

DR. DAUM: Good morning. I'm Robert Daum from the University of Chicago.

DR. FANT: I'm Michael Fant from the University of Texas Health Science Center in Houston.

DR. GAROFALO: I'm Elizabeth

Garofalo. I am the Industry Representative. I'm a Pharmaceutical Consultant.

DR. GORMAN: Rich Gorman, a pediatrician from Baltimore who is the Professional Health Care Organization and non-voting member of the Committee.

DR. HALL: Caroline Hall from the University of Rochester in New York.

DR. HAVENS: Peter Havens, Medical College of Wisconsin in Milwaukee.

DR. HUDSON: Melissa Hudson, Pediatric Oncologist from St. Jude Research Hospital in Memphis, Tennessee.

CHAIRPERSON RAPPLEY: Marsha Rappley from Michigan State University.

DR. PENA: Carlos Pena, Executive Secretary.

DR. KIMBERLIN: David Kimberlin, University of Alabama at Birmingham.

DR. KOCIS: Keith Kocis from the University of North Carolina.

DR. NEWMAN: Tom Newman from the

University of California, San Francisco.

DR. ROSENTHAL: I'm Geoff Rosenthal from the Cleveland Clinic.

MS. VINING: Elaine Vining. I'm the Consumer Representative.

DR. WARD: Bob Ward, University of Utah.

DR. OKABE: Good morning, everybody. My name is Dr. Nobuhiko Okabe. I came from Tokyo, Japan. I work in National Institution of Infectious Diseases in Tokyo and thank you very much inviting me to this very important and interesting meeting. I am very happy and also I would like to join this exciting discussion with you. Thank you very much.

DR. MURPHY: I'm Diane Murphy from the Office of Pediatric Therapeutics at FDA.

DR. McMAHON: Ann McMahon, Office of Surveillance and Epidemiology at the FDA.

DR. LEWIS: Linda Lewis, Medical Officer, Division of Antiviral Products, FDA.

DR. ROTHSTEIN: Adrienne Rothstein, Safety Evaluator with the Office of Surveillance and Epidemiology.

DR. PENA: Thank you and good morning, everyone. The following announcement addresses the issue of conflict of interest with regard to today's discussion of the a report by the Agency on Adverse Event Reporting.

As mandated in Section 17 in the Best Pharmaceuticals for Children Act, the Pediatric Advisory Committee will hear and discuss information on adverse event reports, focusing on neuropsychiatric and behavioral events which were requested by the Pediatric Advisory Committee when the reports were first presented. This statement is made part of the record to preclude any appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the Committee participants, it has

been determined that all interests in firms regulated by the Food and Drug Administration present no potential point appearance of a conflict of interest at this meeting. In the event that discussions involve any other products or firms not already on the agenda for which an FDA participant has financial interests, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

We do note that Ms. Amy Celento is participating as the Pediatric Health Care Representative, Ms. Elaine Vining is participating as the Consumer Representative and Drs. Caroline Hall, Peter Havens and David Kimberlin are participating as Temporary Voting Members for this meeting. We would also like to note as you've heard that Dr. Elizabeth Garofalo is participating as the Non-Voting Industry Representative acting on behalf of regulated industry, Dr. Richard

Gorman is participating as a Temporary Non-Voting Pediatric Health Organization Representative acting on behalf of the American Academy of Pediatrics and, with respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment upon.

We have an open public comment scheduled for 1:00 p.m. I would just like to remind everyone to turn your microphones on when you speak so that the transcriber can pick up everything and turn them off when you are not speaking. I would also like to remind the audience members to please make sure that their cell phones are on silent mode only. Thank you.

CHAIRPERSON RAPPLEY: Dianne.

DR. MURPHY: I need to take just a few minutes to sincerely welcome the Committee and I know you receive a letter every time we

have a meeting telling you how much we appreciate your participation. But I wanted to take a minute this morning and tell you that you may be feeling a little inundated for a good reason.

This will now be the 70th time that we have brought a product to this Committee. This Committee meets at least twice a year. Your expertise is requested a number of other times, the number, you just met the cough and cold products. You are a very frequently requested group of experts and we call on you frequency and we do appreciate it.

What you do with each adverse event review that we send you, we send you a minimum of five documents for review. You just for this meeting are doing seven. If you do the math, 35. We then had -- that's for your abbreviated or your standard review. For anything that is expanded review and we have three products that fell in that category because they've either had safety signals and

we thought the Committee needed to hear background on that or they have an evolving safety issue, you got additional documents. You got 66 documents per Carlos for this review. You have an enormous amount of work that we have asked you to do and we sincerely appreciate the time and effort that you have put into this.

The last time that we -- the last two times that we met, this Committee specifically asked for information in certain areas concerning Tamiflu and these unusual neuropsychiatric adverse events that were being reported out of Japan. I'm not going to list all those to you. They've been listed in your review packets, but so that the public will be reminded, the Committee specifically wanted the Agency and the Company to look at -- try to find patients who were being treated with prophylaxis. You wanted us to look at other databases. You wanted us to look and see if there were any other preclinical

information. You wanted us to look at other countries. You wanted us to look at other antivirals and you wanted us to better explain what was going on in Japan because as you've noted in your use document and a number of the presentations, Japan uses something, 75 or 80 percent, whatever, of this product in the world. We have tried to fulfill all of those requests and we hope to present in a condensed version much of that information to you today.

As has been noted, Dr. Okabe, the Director of Infectious Disease Surveillance Center with the National Institute of Infectious Disease in Japan is with us this morning to give us a better oversight or understanding of what happens in Japan when patients are diagnosed with influenza, what is the background of the epidemiology of influenza in Japan.

We've also asked Dr. Shay from CDC to provide again a very nice summary that he gave previously on what the epidemiology of

influenza in this country is particularly focusing on the Neuropsych Encephalitis.

Dr. Shay had a personal emergency and is not going to be here today. And Carlos assures me we're going to be able to get him on the phone. He is the next speaker. So if you could follow up while I finish talking and make sure that -- Is he on?

(No verbal response.)

He is going to walk us through his slides and be available for questions on the phone. That's the plan. Otherwise, Linda Lewis is going to get up there and walk us through the slides. We're adaptable.

We also wanted to welcome today members from the Pharmaceutical and Medical Device Agency in Japan and Dr. Yamamoto and Ms. Nomura who are also here today. And in addition, I wanted to just to announce to you all that Dr. Julia Dunne, Julia, if you would raise your hand or stand up or whatever, who has been instrumental in helping develop ICH

document on E-11 on how to develop products internationally for children is a member of the Medicine's End Health Care Products Regulatory Agency in England, based in London, and she is on detail to our office for the next couple of years and we are delighted to have her bring her perspective also to the review of these products and to pediatric issues.

After Dr. Shay presents the background on influenza in this country, Dr. Okabe will be providing the Japanese perspective and then Dr. Linda Lewis is going to provide an overview of everything that has happened since 2005, right, or 2005 plus so that we can make sure everybody's on the same page and because we had so many documents we were sending you we thought this would be helpful to do that.

Then Adrienne Rothstein will be presenting the adverse event review and she will be presenting both the deaths, the

document that I talked to you about this morning, and the additional adverse event review document that we sent you covering Tamiflu and other antivirals, adverse reporting for other antivirals in addition to Tamiflu.

Then we have a sponsor presentation from Roche. We do have opportunities for clarification questions. Those clarification questions we would please request be just that. You couldn't understand a fact, would they straighten that out for you and make it clearer what they meant, and not get into the discussion of the questions at that point.

We then have a presentation from Glaxo SmithKline for Relenza. We will have a break. We do have lunch in there by the way. I didn't mention that, but we are going to let you eat and then we will then after all of that go through the questions with you and I think that took up my ten minutes, Carlos. Thank you very much again for being here this

morning and for carrying all those documents with you.

DR. PENA: Do we have David Shay on the line?

DR. SHAY: Yes, I'm here.

DR. PENA: Okay.

DR. PENA: David, will you please tell us when to change the slide?

DR. SHAY: Sure. I will. This is David Shay from CDC's Influenza Division and I'm sorry I'm not able to be there in person today.

This presentation is a background on influenza-related mortality and encephalopathy among children in the United States based on the data that have been collected by CDC. Next slide please.

As you all know, influenza causes annual epidemics of disease and is a major cause of morbidity and mortality, particularly among young children, those age 65 years and older and those with underlying pulmonary,

cardiac and other diseases. Nationally available data about the mortality burden of influenza has its limitations. Relatively few respiratory illness cases are tested and influenza confirmed infections are rarely listed on death certificates. Influenza is generally not a reportable condition in the United States with one exception and we'll spend time talking about that. So for decades, estimates of U.S. deaths and hospitalizations have been made using statistical models and these are in retrospect death certificate data, hospitalization discharge data and viral surveillance data. Next slide please.

Modeling studies conducted in the past decade or so estimate an annual average of approximately 200,000 influenza-associated deaths per year and about 36,000 influenza deaths per year. These average numbers, however, hide considerable variability in the year to year burden of influenza. For

example, H3N2 seasons are typically associated with more severe disease and in the `90s were associated with up to 50,000 annual deaths in the United States annually, while the low end of mortality that we've seen might be on the order of 16,000.

The highest rates of complications of influenza infections we've seen in persons again with pulmonary and cardiac disease, the older individuals and the youngest. Mortality data for children due to influenza has been very limited in the past. However, modeling studies have estimated an average of approximately 92 influenza-associated deaths among children aged less than five on an annual basis. Next slide please.

Many of you are familiar that 2003-2004 season was a severe one and particularly among children in the United States. It was also characterized by the fact that it began very early, as early as October, in some states. H3N2 viruses were the predominant

subtype and again those have been historically been associated with more severe seasons. There was a relative vaccine mismatch for the H3N2 strain that year and CDC began receiving reports of influenza-related deaths in children in November of 2003. At that time, we had no really comparable historical data. There was a great public concern of vaccine shortages in several areas of the country that were experiencing an early season. So on December 13, 2003, CDC made a request to state, territorial and local health departments for reports of pediatric influenza-associated deaths. Next slide please.

And the surveillance period for this reporting was from September 28, 2003 to May 22, 2004. The case definition was a death in a U.S. resident age less than 18 years old in that surveillance period with evidence of an influenza virus protection by about at least one laboratory test and those included

were rapid, commercially available and they did detection test, IFA, culture, RT-PCR or aminohistochemistry on autopsy specimens performed at CDC. Next slide please.

So here are the results from the `03-`04 season. One hundred fifty-three deaths were reported from forty states. The median age of these children was three years with a range from two weeks through 17 years. Half were male and among those children from whom race data were available, 67 percent were white, 22 percent were black, six percent were Asian and among that proportion for whom ethnicity data were available 24 percent were Hispanic ethnicity. Next slide please.

This slides shows the methods of diagnosis for influenza among the 153 children. Rapid antigen detection tests were used to diagnose influenza in a total of 117 children. This was the sole method of diagnosis in 57 or 38 percent. Viral culture was the sole method of diagnosis in 11

percent, RT-PCR in three percent, fluorescent antibody test, either direct fluorescent antibody or indirect fluorescent antibody in three, immunohistochemical staining again on autopsy specimens in three and multiple methods were used to diagnose influenza in 41 percent of these children. Next slide please.

This slide shows the epidemic curve of influenza activity in that season and the death and what is notable in the red line there shows the viral circulation. If anything, viral circulation peaked before the peaks in reported deaths based on data of onset of illness, probably reflecting again the fact that a request for reporting was not made until the season had begun in the United States and if anything this total of 153 would likely therefore represent an underestimate of the number of deaths that occurred in the United States that season. Next slide please.

This slide shows the age distribution of the 153 children. Not

surprisingly, most of these children were relatively young with the greatest proportion either being less than a year of age or a year of age. But I also note that there are reports of deaths for children in each age category greater than nine years of age, so not restricted solely to young children. Next slide please.

This slide provides the age specific mortality rates. The highest rate of mortality was seen in the youngest children, those with age less than six months for whom vaccinations is not currently licensed and the rate there was 0.88 per 100,000. For six to 23 month children, the rate was 0.71. For children two to four years of age, it was 0.3 and for the oldest children, five through 17, it was 0.11 for an average for the whole group of 0.2 per 100,000. Next slide please.

This shows the mortality rate information graphically and it shows basically a decreasing rate with increasing age group

and this diagram is from the paper by Norwich and Bott that was in the New England Journal that summarized these data. Next slide please.

When we looked at chart review information that was available for these children, there was quite an effort made in this season to go back and acquire partial or complete medical records with the help of the state health departments whenever possible. So when we looked back at these children, 45 percent were otherwise healthy children. A short proportion had unknown health status. Ten percent had an ACIP high risk condition, so cardiac pulmonary disease, metabolic disorder as well as Melcourse was the most common among children at this time.

Further, 22 percent had an ACIP condition plus any indication in the medical record that they had any other chronic medical condition for which a vaccination was not recommended at that time and 20 percent of

these children only had an non ACIP chronic health condition. Next slide please.

This slides shows the location at time of death of these children. Fifty-nine percent were in the inpatient hospital bed or an ICU bed. A substantial proportion, however, either died at home or in transit, 31 percent, or while being evaluated in an emergency room, ten percent. Next slide please.

This slide and the one after it summarizes the reported clinical and autopsy diagnoses on these children. Again in this particular year we were able to go through the records and a pretty complete detail compared to the information we have available subsequently. And among these children, the most common diagnosis was pneumonia with 71 of the 146 children for whom there was information available. Other notable diagnoses included pneumonitis in 13, bronchiolitis in 10, Acute Respiratory

Distress Syndrome in 10, croup in six and some sort of indication of trachelitis or bronchitis again mainly in children who were intubated in 27, some indication of systemic illness such that shock was also present in a substantial proportion of these children, 43 with sepsis syndrome, 33 with a diagnosis of shock somewhere in the records. Next slide please.

Now when we look at neurologic conditions that were diagnosed in these children, encephalopathy or encephalitis was present in 13, stroke in six and seizures in 14. Other notable diagnoses included myo- or peri-carditis six, myocardial infarction in two, and DIC in 18, hemophagocytosis syndrome in three. Next slide please.

This slide again shows a table from the Bott paper that looks at bacteria co-infections in 24 children for whom there was a definitive date available. The most common was Staph aureus in 11 children. Six of these

were Methicillin resistant, one Methicillin susceptible, four had unknown susceptibility, three were Staph species not otherwise specified, excuse me, one was Staph not otherwise specified, Strep pneumo present in two, Group A Strep in three, and a Bordetella pertussis in one, each flu in four children and a variety of other gram negative pathogens in a single child each. Next slide please.

This slide looks at antiviral medication use for these children. So there were a total of 153 deaths. Antiviral status was unknown in 25 percent. We did have information available from the medical records of 75 percent of the children about medication they had received and of those, 26 or 23 percent had received an antiviral agent and the median was one day with a mean of 2.6 days of receipt of medications.

Eighty-nine or 77 percent had not received an antiviral. Those children who had received an antiviral, the most commonly

prescribed agents were oseltamivir in 12 and amantadine in 12 or amantadine in two and none of the children had received zanamivir. Next slide please.

So some of the limitations of these data is that again a request for case reports was made near the peak of the season in December. It was a passive surveillance system, really an enhanced system but still a passive surveillance system. We know that there were variations in testing practices, in clinical and pathological diagnoses that were made and about how those bits of information were sent to CDC.

We had problems with incomplete medical records and there was very limited information available, of course, for the nonhospitalized cases. We also had a lack of comparable data from subsequent seasons as well. So this is our most complete pediatric mortality. Next slide please.

This describes the pediatric --

CHAIRPERSON RAPPLEY: Dr. Shay.

DR. SHAY: Yes.

CHAIRPERSON RAPPLEY: Can I interrupt you? We're having trouble hearing and we're getting some loud static.

CHAIRPERSON RAPPLEY: Yes, I can hear that.

CHAIRPERSON RAPPLEY: Okay. We're trying to fix it on our end and I guess if you can stay close to the mike we'll see what we can do.

DR. SHAY: Okay.

CHAIRPERSON RAPPLEY: So keep going. Thank you. Sure I'll just start over with this slide.

So after this --

CHAIRPERSON RAPPLEY: That's much better.

DR. SHAY: Okay. So after this season, the Council of State and Territorial Epidemiologists met and agreed to make laboratory confirmed pediatric influenza

associated deaths in nationally --

(Telephonic interruption)

-- condition. This was voted on in a meeting in June 2004 and the reporting began in 2004 and these data are now reported weekly in MMWR and then our weekly influenza update.

It is a traditionally nationally notifiable condition now so that fewer data elements are collected in a two-page reporting form. Not every state has adopted the pediatric reporting for influenza. Forty-two states currently comport to the nationally notifiable condition for that reporting locality. Next slide please.

So this summarizes the data from the last season. We had 47 cases reported from 18 states during the 2004-2005 season. One child had received antivirals during that season and that child received oseltamivir. The next season we had 45 cases reported from 14 states during --

CHAIRPERSON RAPPLEY: Dr. Shay.

DR. SHAY: Yes.

CHAIRPERSON RAPPLEY: We are going to try and recall you. Is that correct?

PARTICIPANT: Yes.

CHAIRPERSON RAPPLEY: So he should just hang up.

PARTICIPANT: Yes.

CHAIRPERSON RAPPLEY: Dr. Shay, if you would please hang up, we are going to try and reconnect with you because it's hard to concentrate when there is this shattering noise going through.

DR. SHAY: I appreciate that.

CHAIRPERSON RAPPLEY: Okay.

DR. SHAY: Okay. I'll hang up now.

CHAIRPERSON RAPPLEY: If you'll hang up please. Thank you.

DR. SHAY: Sure.

(Pause for reconnection of line.)

CHAIRPERSON RAPPLEY: This is like the airline pilot update. When he recalled, he could still hear it on his phone. So he

thinks it's his phone. At the moment, he is trying to get another phone. How long do you think that will take us?

(Off the microphone comment.)

CHAIRPERSON RAPPLEY: Five minutes. I guess if everybody doesn't -- Do you want to take five minute break? Let's take a five minute break and please so -- This is so we can shorten your break in the future. Thank you. Quarter of by my watch be back. Off the record.

(Whereupon, at 8:38 a.m., the above-entitled matter recessed and reconvened at 8:44 a.m.)

DR. SHAY: This is David. Would you like me to start?

CHAIRPERSON RAPPLEY: Can you please remind us which slide you're going to resume with?

DR. SHAY: Sure. It's slide 20. The title is "Pediatric Influenza Mortality Reporting System."

CHAIRPERSON RAPPLEY: Okay. Thank you.

DR. SHAY: Okay. Sorry about that. I guess we're back. Again, in the first season of this pediatric mortality reporting system, we have reports of 47 cases of death from 18 states. Only one of those children was noted to have received oseltamivir. But again, this was a shorter, two-page reporting form and we did have access to the complete medical records.

In the second season, 2005-2006, there were 45 cases reported from 14 states. Three of these children had received oseltamivir and one rimantadine. In the past season, 2006-2007, there were 71 cases reported from 26 states. Three of those children received oseltamivir and one just an indication that an antiviral agent was received with no other information. Next slide please.

So that summarizes the information

that we have available, the deaths from influenza and the relationship to receipts of antiviral agents. Next we'll talk briefly about influenza-associated acute encephalopathy in children, again from data reported from the 2003-2004 season. Next slide please.

So influenza-associated encephalopathy is an uncommon complication of influenza infections, can result in serious neurologic sequelae, has most commonly been reported in young Japanese children. For example, 48 Japanese cases were reported during 1998-1999. There are only 25 --

CHAIRPERSON RAPPLEY: David.

DR. SHAY: Yes.

CHAIRPERSON RAPPLEY: Hold on for one second. He's going to switch cables.

DR. SHAY: Okay.

CHAIRPERSON RAPPLEY: Try it again please.

DR. SHAY: Sure. So continuing the

25 U.S. cases of IAE were reported to CDC during the 1999-2003 seasons. Next slide please.

Again in this severe influenza season in children, there was a request made for enhanced surveillance from the state health departments. The surveillance period was again September through May. The case definition was a U.S. resident in age less than 18 with a febrile illness that was laboratory confirmed as influenza who had altered mental status. Next slide please.

Case definition of a probable case was altered mental status for more than 24 hours and onset of altered mental status within five days of the onset of fever and no other cause identified in this child for an altered mental status. Next slide please.

There was also a suspect case definition which was defined as duration of altered mental status was unknown or altered mental status was greater than 24 hours, but

another cause was unable to be ruled out, for instance, a child with an existing underlying seizure disorder or altered mental status less than 24 hours or another cause of altered mental status identified but with either status Epilepticus or objective findings of a cerebral inflammation like a CT or MRI finding. Next slide please.

So there were 42 cases reported from 22 states in this season. Twenty-two were probable. Twenty were suspect. Forty-eight percent of these were male, fifty-four percent of the probable case and forty percent of the suspect. Next slide please.

Where we had information on race, 50 percent of the probably cases were white and 67 percent of the suspect cases. Thirty-three of the probable and suspect cases were black. And only three or 17 percent of the probable cases were noted as Asian or Asian Pacific Islander and none of the suspect cases. Next slide please.

Ethnicity information was available on some of the children probable in 13. One of these children was Hispanic in for 13 of the suspect cases and 38 percent of these cases were Hispanic. Next slide please.

Can you hear me?

CHAIRPERSON RAPPLEY: Yes, we can hear you.

DR. SHAY: Okay. So this information on the age distribution of these 42 children and note that in contrast to the pediatric mortality, it's sort of a more even age distribution. There might be some indication that in children less than five there are more cases but again not the same peak we've seen for the pediatric death cases. So it's spread fairly evenly throughout the pediatric age range. Next slide please.

When we look at underlying high risk medical conditions for these 42 children, 27 had no prior medical conditions noted in the available records, 15 had at least one

chronic medical condition, seven of the probable and eight of the suspect cases, and five had a condition for which ACIP recommended influenza vaccination for the 2003-2004 influenza season. Next slide please.

These specific medical conditions were chronic GI conditions. That was chronic malabsorption not well defined in one, arthritis in one child, one child had chronic lung disease, two with cerebral palsy, two with seizure disorders, two with ENT abnormalities, three had asthma and six of these children had developmental delay and the conditions ranged from moderate developmental delay to serious developmental delay. Next slide please.

This slide shows the time from fever to onset of encephalopathy and in general, it was zero-one or two-three or three days and not much difference by a probable or suspect case definition. Next slide please.

Clinical definition presentation of these children, 33 or 78 percent presented with altered mental status with a median duration of three days and a range of one to 31 days among 28 patients for whom there were available data. Twenty or 48 percent of the children had seizures, nine of the probable and 11 of the suspect. Eight had status Epilepticus and 16 including those eight had some sort of multiple seizures while under medical care. Next slide please.

Forty percent of children had a movement disorder or ataxia noted, eight of the probable and nine of the suspect and also noted in there was decreased strength or flaccid weakness, hypo- or hypertonicity, slow movements or unable to hold the trunk or the head properly. Next slide please.

This slide summarizes the neuro-imaging studies that were available on these children. Twenty-six had an MRI done. Sixty-five percent of those were abnormal.

Seventeen of the probable cases had an MRI and 11 were abnormal, nine of the suspect and six were abnormal. The abnormalities included cerebral edema which was the most common and also evidence of an infarct tonsillar herniation or an focal cerebritis. Next slide please.

Eleven children had only a CT scan available, three of the probable cases and one was abnormal, eight of the suspect cases and three were abnormal. All four of these abnormal CT showed cerebral edema, two with evidence of herniation. Next slide please.

Diagnostic testing of these children, 71 percent had CSF studies available, 18 of the probable cases and seven had evidence of greater than or equal to five white blood cells per millimeter in the CSF and the range was from 8 to 67 cells, 13 of the suspect cases, but only one had greater than five white cells. One influenza -- There was a positive culture for influenza from one

of the 17 CSF specimens that were cultured for viral agents. Next slide please.

Looking at the antiviral medicines, these children received, 20 received antivirals, 10 of the probable cases. Ten received oseltamivir and one received rimantadine as well as oseltamivir. Ten of the suspect cases, four received oseltamivir, five amantadine and one rimantadine. Next slide please.

This slide looks at the information we had available on the timing of the antiviral treatment to onset of symptoms. Before onset of neurological symptoms, none of the probable and only one of the suspect cases was documented to have received an antiviral agent. On the day of development of neurologic symptoms, it's difficult to say more, two of the probable and five of the suspect cases received their first dose of an antiviral and clearly after the development of neurologic symptoms, eight of the probable and

four of the suspect cases first received a dose of antiviral agents. Next slide please.

The outcomes of these children, 19 recovered without neurologic sequelae, 10 of the probable and eight of the suspect, actually 11 of the probable and eight of the suspect cases. Thirteen recovered with chronic neurologic sequelae, eight of the probable and five of the suspect cases. Seven died, four probable and three suspect and the status was unknown despite attempts of followup for three of the suspect cases. Next slide please.

This slide looks at the outcome of these children by age group and it's showing that for each of the age groups studied there were some children who recovered with neurologic sequelae and that the children who died were predominating in the one to four and 10 to 17 years old age groups. Next slide please.

So the limitations of this series

of patients, this was again a passive surveillance in the severe flu season at least among children. It's likely that some cases were missed. We know that there was evidence of selection or referral bias here because some states were much more likely to be able to report this type of information than others. Again, there was substantial differential reporting by states despite attempts throughout the season to contact each of the states on at least a weekly basis.

Again, the timing of the surveillance, the request for cases was not made until approximately after the peak of the season. There's limited clinical data available for many of these children and today we still have no national system to collect data on laboratory confirmed cases of encephalopathy that appear to be associated with influenza virus infections. Next slide.

So in summary, during this season, there were at least 42 cases of acute

encephalopathy, 22 probable and 20 suspect in the case definitions that were used here. Asian American ethnicity was not a prominent feature in this season among the children who were reported to us. Fifty percent of the children were less than five years old, but older children were also affected and compared to again the mortality cases more notably 20 of these children had severe outcomes including death or chronic neurologic sequelae. Next slide.

And this is a slide that acknowledges all the people who provided the data that are summarized here in this report. Thank you for your attention and I'm sorry for the difficulties and I'd be happy to try to answer any questions that you may have.

CHAIRPERSON RAPPLEY: Thank you, Dr. Shay, and I think your last slide just illustrates the number of people in the person power that's required to put this kind of information together. So thank you for

acknowledging all of those people.

We are open for clarification questions now. Yes, Rob.

DR. WARD: On the diagnostic criteria testing, could you tell us whether the CSF was adjusted for red cells or how many of these had a large number of red cells with it?

DR. SHAY: I don't have that information right in front of me, but there were no bloody taps here.

DR. WARD: Okay.

DR. SHAY: So that the information that is available, again I don't have the precise figures in front of me but either no or scant red cells present.

DR. DAUM: Thank you for your presentation. I have three short clarification questions. The first one is from the children that died is there any post mortem data with regard to viral studies and the CSF or the brain.

DR. SHAY: No, there are not. That information is not available.

DR. DAUM: The second question is when you were formulating the definitions of the suspect or probable how did you handle the instance of a septic child. Were they -- Or presumed septic child because they could certainly have encephalopathy from that process and did you make any adjustment for that?

DR. SHAY: That's a very good question. Those children who would have fit into that category had another reason to have altered mental status.

DR. DAUM: Even if it was like suspected sepsis because most of your sepsis if I saw the slide right was suspected and not proven.

DR. SHAY: Yes, you're right. Those were clinical definitions. Those are in the children who died. There is some overlap in children who died with encephalopathy and

in the encephalopathy-only cases.

DR. DAUM: So these are nonseptic kids.

DR. SHAY: That's correct.

DR. DAUM: And my last question is I'm sure the answer is going to frustrate us but I'm going to ask anyway. Are there any denominator data, any sense of the denominator, of how often this occurs? How rare it is from your surveillance?

DR. SHAY: It would appear to be a very rare case in the United States and certainly compared to -- The only thing I think I can say for certain certainly compared to influenza-associated mortality it definitely appears to be less common than that outcome. Despite the fact that every state, for example, only 42 of 50 states have made the pediatric influenza-associated mortality a reportable condition. We have received reports from states for whom it's not a reportable condition. We don't have sort of a

similar system for encephalopathy but we have encouraged states to report whenever they hear of a case and we just do not have the same number of reports coming to us through our tradition contacts in state and local public health departments as we do in the mortality. It's a frustrating answer, but I think I can say it appears to be less common than the more severe outcome of mortality.

DR. HALL: David, this is Caroline Hall. Thank you for a nice presentation. I have just one very quick question. In your enhanced surveillance methods slide, you mention that the case definition includes laboratory-confirmed influenza virus infection. Was that confirmed by one of the rapid tests or whatever you presented in the earlier portion or does that mean at any time during the case exploration or definition whether it's pathologic or any other sort? Is that all laboratory confirmed meaning the RTPCR and the three methods that you gave in

the earlier slide?

DR. SHAY: I'm sorry. I had a very difficult time hearing the last question. Before I answer, could it be repeat?

DR. HALL: My basic question is in the laboratory-confirmed definition what does that include. Would that include pathologic confirmation, histological or is that all the initial laboratory RTPCR, IFA, rapid antigen tests?

DR. SHAY: Yes. I have -- it includes both. I mean, in the mortality series, there were a few cases that were diagnosed solely by pathological specimen three I believe with aminohistochemical testing conducted at CDC. Those cases were reported because there were unexplained deaths that were then subsequently found to have evidence of influenza infection only by pathologic testing. All the other cases reported here had positive clinical specimens for influenza virus infection.

DR. HALL: And were before death then.

DR. SHAY: And were before death. That's correct.

DR. HALL: I see. Thank you.

DR. ROSENTHAL: I have a question regarding the subset of patients who both died or a subset of subjects who both died and received antiviral medications and my question has to do with that there are two time intervals that are interesting. The first is the time between onset of symptoms and administration of an antiviral and the other is the time between antiviral administration and death and I'm wondering if you can clarify anything regarding these times for this subset.

DR. SHAY: Thank you. That's a great question. Unfortunately, we don't have that information in most of these children. You recall that the median and duration of treatment and antiviral is only about a day

and when going back to the available records, they often times didn't have enough information from, for instances, pharmacy records to be able for the children who are hospitalized to be able to break that down into much finer detail.

DR. WARD: David, could you clarify in the CSF studies how they correlated with the children who had evidence of cerebral edema, whether there were cases with negative CSF studies in the children with imaging evidence of cerebral edema and visa versa. That is positive CSF pelocytosis without evidence of cerebral edema?

DR. SHAY: Yes, I believe so. Again, there were only 17 cases I believe for whom CSF were available. Now let me go to that slide. No, there were 31 cases that had CSF studies done. That's correct. And so there were some cases. I'm afraid because of my circumstances I don't have the complete data in front of me right now, but I can get

the answer for you in a day or so.

DR. LEWIS: David, this is Linda Lewis and, first of all, I just want to say how much I appreciate the fact that you were able to call in and give you talk and I didn't have to do that. But I did have one question about the relevance of this data to the adverse events that we will be exploring further in later talks.

It appears to me that patients who had relatively brief periods of abnormal mental status or abnormal behavior would have potentially been captured in the suspect case category. Am I interpreting that correctly?

DR. SHAY: Yes.

DR. LEWIS: Thank you.

DR. WARD: Around the table, we have a lot of very skilled biovirologists. Could one of you address why the CSF cultures for influenza seem to be very low compared to the number of cases, only one positive out of 17 reported here?

DR. HALL: Well, again, Caroline Hall. This goes back, I think, and David can confirm this to the type of test that is being utilized in order to get it into the -- I mean, you can look at it in two ways. CSF could be positive by RTPCRV if it were simply viremic and that's why I was sort of asking what kind of diagnosis method that was used in RTPCRV. So sensitive, the disease may have occurred some time earlier and not been related.

In terms of a pelocytosis with direct invasion, if that's what you're meaning, I cannot explain, of course, why that would not be positive except to say that this is probably not a direct invasion process influenza which has been suggested in some of the other materials that we have received and I think others may confirm that.

DR. KIMBERLIN: And I concur that Dr. Murashima and others in Japan have described what likely is more of a cytokine

type of an effect of the central nervous system as compared to a direct viral invasion.

DR. HALL: Right.

DR. OKABE: Can I make some comments? Because from our experiences there are so many inferences, so called encephalopathy not encephalitis and post mortem examination and also the CSF virus culture. Not all, but most of them are negative. So it is difficult to say the directing vision occur for this inference as -- statement.

DR. NEWMAN: Just to, this is Tom Newman, clarify the answer to Linda Lewis' question because I sort of have the same question. If someone had altered mental status less than 24 hours, it seems like they also had to have either status Epilepticus or objective findings of cerebral inflammation. So it seems like that might not include a very large number of the ones who had transient mental status changes. Is that right?

DR. SHAY: That's correct. They had to have for those children who had altered mental status for less than 24 hours they had to have other objective signs. That's correct.

DR. NEWMAN: Do we have any idea like how many there were, how common that was to have several hours of altered mental status changes? Maybe it will come up later from the Infectious Disease experts.

DR. SHAY: It's not common. There were few children who had, for instance, only several hours plus one of these other findings.

CHAIRPERSON RAPPLEY: So, Dr. Shay, could you just summarize for us the ability of this dataset to capture those kind of unusual behaviors that characterized why we're meeting and having this question today about the adverse neuropsych events? Does this dataset about morbidity and mortality capture those behavioral symptoms?

DR. SHAY: This dataset is about morbidity and mortality and when possible some indication of when the timing of antiviral agents was in relationship to those severe outcomes. This dataset does not nor was it designed to capture all, for instances, unusual behavioral manifestations that might be associated with influenza infections.

CHAIRPERSON RAPPLEY: Yes, another question.

DR. OKABE: Make a comment. The very early stage of the influenza in a child shows some abnormal behavior such as crying suddenly or say something unknown or convulsions and also a scare. But death has been recognized before using the Tamiflu therapy. These are definitely observed as your early stage of influenza and several pathways without any kind of a treatment.

CHAIRPERSON RAPPLEY: Thank you. Any remaining clarifying questions? Yes.

DR. KOCIS: Just going further with

the seizures and the altered mental status for less than 24 hours and some of the documents that talk about febrile seizures and confounding of that, I guess, not specifically this but as we think further about how one might, could or couldn't separate the typical febrile seizure in these kids from these more serious CNS anomalies and how you define status Epilepticus.

CHAIRPERSON RAPPLEY: Was that a question or a statement?

DR. KOCIS: That was a question.

CHAIRPERSON RAPPLEY: So that was a question you would like Dr. Shay to --

DR. KOCIS: Yes. I think was there a way or are we just going to accept that we're going to have a lot of confounding with these relatively minor, i.e., the brief seizure, altered mental status which would quickly resolve and therefore can we separate the two, the serious CNS from the more common febrile seizure.

DR. SHAY: Obviously, that was the intent of the suspect case definition and why it's relatively complicated. To try to tease out simple febrile seizures associated with an influenza infection in these children from something that looked more serious, I don't think we're going to do better than what we've tried to accomplish here and again this is worth noting again just because of the rare condition in the United States. We have not heard about, despite attempts to reach out to our partners, subsequent to this season about large numbers of cases that would meet either these suspect or probable case definitions in the United States, again despite hearing about fewer but substantial numbers of cases of mortality each of the subsequent seasons.

CHAIRPERSON RAPPLEY: Any more questions?

DR. HALL: Yes.

CHAIRPERSON RAPPLEY: Okay. Go ahead.

DR. HALL: David, again I'm trying to identify those that had the simple febrile seizures. Have you tried it in terms of looking at the number that actually had fever who were between, say, six months and three years of age, the classic findings that occurred at the first or maybe second day of fever? Do you have that kind of information because that would help and that were not recurrent seizures? Again, it would be atypical for the febrile seizure.

DR. SHAY: Right. I can't -- I wasn't able to hear all of the question. But I think it was again trying to separate out the simple febrile seizures from more serious. I mean, the definition that we could use is status Epilepticus, for example, was based on what was in the chart. This was based, obviously, on retrospective chart review and not prospectively. So for a suspect case, they would either have, those that had altered mental status less than 24 hours, status

Epilepticus noted in their medical record or objective findings of cerebral information. So that was the attempt there to separate out if I understand your question to be just simple or recurrent febrile seizures.

DR. HALL: Do you have though the number that actually had fever and they're putting that together with their age and having it occur on the first or second day of illness? Do you have that kind of information?

DR. SHAY: All the children had fever to be eligible to be in this case series. What I don't have in front of me right now the detailed information that you're asking for.

DR. HALL: Thank you.

CHAIRPERSON RAPPLEY: Any remaining questions?

(No verbal response.)

CHAIRPERSON RAPPLEY: Dr. Shay, again we say thank you very much for your

patience and for participating from home and we'd like to move on then to the presentation from Dr. Linda Lewis -- No?

DR. LEWIS: No, we're going to Dr. Okabe next.

CHAIRPERSON RAPPLEY: I'm sorry. Okay. I was going by the old one. Okay. Dr. Nobuhiko Okabe. Dr. Okabe is Medical Officer in the Division of -- Excuse me. He is the Director of Infectious Disease Surveillance Center at the National Institute of Infectious Diseases in Japan.

DR. OKABE: Okay. I don't use it. Excuse me. It doesn't work.

(Off the record discussion.)

DR. OKABE: Thank you very much. My name is Dr. Okabe from Tokyo, Japan and I'm very happy to talk about on influenza and influenza encephalopathy and also some relation to Tamiflu. The organizers asked us to give three stories. One is the seasonal regular influenza status in Japan and how to

collect the information. The second is the present status of the influenza encephalopathy and also the third story is for the present situation of Tamiflu in Japan and the next slide please.

So I'll take this opportunity to show a little bit about my institution, the National Institute of Infectious Diseases. Next one please.

One component is NIH-like function. So basic research and development is done. And the next one.

The second function is a CDC-like function, disease control and prevention. Myself is involved for the CDC-like function and the third component is the FDA-like. So there are quite a few people to these three components in my country. The next one please.

And this is the organization of NIID. There is so many units or divisions and we have for influenza, one is Department of

Virology III. Dr. Masato Tashiryo is the director of this division and to look at about the influence of virology study. And my unit called Infectious Disease of the Center and Influenza issue is one of the big issues that we have to do. The next one please.

And this is very typical efficiencies we have in our system. So if the doctors recognize some targeted diseases so doctors report to their local public health center in pre-infectious level and this information is transmitted to their local government and the information transmitted to the central government which is Ministry of Health and Welfare and this information is also transmitted to our NIID and we collect the information. But if they put the data in a computer or some other instrument, we can access this data in on-time and also the other role is the local public health laboratories, if it is necessary for the public health purpose that doctor can send the specimens to

the local public health laboratories and data is analyzed. For example, the influenza, most of the influenza is diagnosed by the clinic, but the doctor uses the rapid test kits now. But some of the specimens can send to the local public health laboratory to confirm the virology and the culture or pCL will be done in here. Next slide please.

And targeted diseases or national infectious disease -- are provided and classified by the Infectious Disease Control Law and it was updated in 1999 and revised two times in the past. One is 2003 and the second one was done in 2007, this year, in April. Next one please.

Regarding with the influenza, influenza reported from the sentinels and this is designated as category 5 and the influenza sentinel total number is 5,000 including 3,000 pediatrics and 2,000 internal medicine for adult cases. This information comes in a weekly basis to us and we can make our

analyses. The other sentinel is here, for example, pediatric sentinel, -- sentinel, special designated sentinels, etc. Next one please.

And with regards for the inference on encephalopathy, we don't have the national level -- system before. But recently acute encephalitis syndrome is including for the category 5 diseases. So every doctor who diagnosed influenza encephalopathy, it could be reported through this system. Next one please.

And with regards for the Avian influenza virus infection, it is categorized into the category 4. Next one please.

And if we find -- There is no cases of 4s at the moment. a human case of H5N1 infectious disease will be found, it is used as a category 2 level diseases and patients should be admitted into class 2 infectious disease hospital until recovered. This is a human case of H5N1. So this is not pandemic

influenza. Next one please.

This is National Epidemiological Surveillance for Infectious Disease, we call it NESID, based on the law and for the influenza, as I told, this is a sentinel reporting system. So randomly we selected 5,000 sentinels, 3,000 pediatric practitioners and 2,000 general practitioners make a report as the sentinels and a weekly patient number by age group is done and it is based on the clinical case definition such sudden onset fever, sudden onset fever more than 38 degrees Centigrade and upper respiratory infection symptom and a general symptom. But recently, most of the doctors like to use the rapid diagnosis test. But that is not involved for the case definition on rapid test kit diagnosis. A weekly reported number per sentinel as an index of activity on public health center area prefecture and national level. Next one please.

With regards, the inference of the

surveillance system, we have three pillars. One is mobility surveillance by necessity system, as I talked -- and the second is microbiological surveillance and ten percent of influenza sentinel appointed as a level 3 diagnosis sentinel and they send the specimens to the local public health laboratory to the confirmation of the influenza virus infection and also that the information could be used for the selection for the next season's influenza vaccines. Also the serological surveillance is done which means antibody pre-virus the sera collected from the normal human population and we can obtain the information of the antibody previrus among the normal populations.

Besides these three pillars, the other system is here. Early warning system based on public health center level and also this is very unique. A very rapid reporting system is done among the pediatric practitioners. Three hundred fifty sentinels

all over the country is involved and they are reporting using a website entry system and mostly based on the rapid antigen detection kits. And also we obtained the information from the school absentee surveillance and also the excess deaths are estimated. Next one please.

This is a patient number of influenza per sentinels by a week of the year divided by every year. So, for example, last season in 2007, the season started later than the other years but peaked in the middle level in maybe April, no, the middle of May and lasted naturally, and flat in the summer season, but we can find more in detail this year. Even though the summer, we had influenza particularly in Okinawa-Hokkaido area and this year the season has been started earlier than other years. We can take the information. This kind of influenza information from the sentinels mainly. Next one please.

And this is the impact of seasonal influenza in my country. This is a reported number from sentinel, an estimated number of the total influenza patients and also the excess death is here. So, for example, in the 2002 and 2003 season, 1.18 million reported from the sentinels and the estimated number is 14.850 million and the excess death number was 11,000 at that time. The population in Japan is 130 million. So very roughly about ten percent of the Japanese population suffered by the influenza every year. Next one please.

And this is influenza death by age groups in Japan and that in 1996 it was peaked. This is a case number divided by age group. So it is easy we understand it that most of the death occurred among the senior age population. But the level of the number of the deaths is now decreasing down if compared for the past time. Next one please.

And this is a virus, the influenza virus isolated in the local public health

laboratories and we collected this kind of information at the national level. In the last season, the major was influenza A(H3) and the second one was influenza B, 40 percent, and around 10 percent was A(H1N1). The total number isolated in the local public health laboratory is around 5,000. So, of course, it depends on the season and this is a figure for the last season. Next one please.

The next topic is influenza encephalopathy in Japan. In 1995 and also in 1998, many child death associated with influenza were reported in Japan and in 1999, Japan Ministry of Health and Welfare had determined to organize the collaborative study group and the chief investigator is Professor Doctor Murashima and I serve as one of the members of the group and at this time, of course, no antiviral influenza drugs were used in the market.

In 1999 to 2002, in this group, the most activity was to investigate the

epidemiology, virology, clinical features, pathology in autopsy cases and an extra term in 2003 up to now and the activity is to investigate pathogenesis, genetic background and to complete the guideline for management of influenza acute encephalopathy, IAE. Next one please.

This is annual reported cases of influenza encephalopathy and the right side is just the seasonal influenza trend as I showed before. This is a case number. In 1998 to `99 season, 217 cases and 109 cases, 63, 117, 160 and 102, 119 and 119. So this is the reported case to the research group and we estimated that the 100 to 500 cases per year occurred as acute encephalopathy associated with influenza in Japan. Of course, the number is depends on the influenza outbreak situation. Next one please.

This is a prognosis of influenza encephalopathy. It was done, that is not written, but maybe 2000 to 2003 in the

beginning stage. I was also a pediatrician before coming to the NIAID. But this is very serious and the doctor in the pediatric scene, the emerging room, was very busy in the influenza season. This color indicate without any sequelae, forty-four percent, and this color indicated for the death cases of 30 percent and severe sequelae nine percent and mild sequelae shown as 17 percent. Next slide please.

So this is not Japanese or English, but the font really changed.

(Laughter.)

DR. OKABE: Maybe the age distribution divided by the severity. So most of the peak is the one years old. This is a case number and age group, one years old, two years old, three years old and four years old. And most of them occurred among the young children from one year old to five or six years, before school entry. But not so many cases, but we also could find at the school

age group, even 14 or 15 years old. And most of the severe cases also they gathered in the young age groups. Next one please.

This is the onset from the fever.

And this is the onset of the time, I mean, the wheezing 24 hours from the fever. It indicates at zero and the one day within the 24 days this is indicated for the two days, three days and four days and more. So I would have to say most of the cases occurred within 24 to 48 hours within the fever, excuse me, after onset of the fever. Next one please.

This is brain CT findings and divided into four categories. Most of them show the CVF edema, an extremely severe outcome and acute necrotizing encephalopathy or intracranial hemorrhage with DIC type. We call it HSES. And also brain atrophy also found but it indicates also they're severe. Brain atrophy with prolonged seizures, we sometimes observed in some infants. Next

slide please.

And the pathology of influenza in several -- it was gathered of the report from 20 autopsy cases. Severe brain edema without inflammatory cell infiltration and damage of the blood vessel or vascular endothelial cells, mild pathological change in lower respiratory tract and the virus associated hemophagocytosis was found in one-third of the patients, a fatty degeneration of the liver similar to Rhys Syndrome in some cases, but not most. The virus antigens could not be detected in the CNS and the rapid progressive apoptosis was found in nerve tissues and the liver. The activation of astroglial cells was found in the cases including sudden death cases. Next one please.

This is cytokine levels in the sera of influenza acute encephalopathy patients. It was Dr. Ichiyama in the Yamaguchi University and Group A indicate a poor prognosis group and B indicates a good

prognosis group, C indicates for the febrile covergent group, and D indicates for just influenza. And interleukin 6 SDNF R1 and IL 10 indicates here that these kind of the cytokines in higher amount A group which means a poor prognosis of acute influenza encephalopathy. Next one.

So the other group think about this kind of a figure. So influenza virus invaded in the children and some of the children shows very high hypercytokinemia and also the vascular endothelial damage occurred and apoptosis or hemocytosis in SIRS-like diseases occurred. At this time, severe brain edema or plasma influence to brain tissues and also the acute necrotizing encephalopathy occurred, etc. And the final, multiple organ failure rarely occurred. Next one please.

And the other group shows the recommendation on treatment for the very severe cases, the use of anti-influenza drugs to reduce the viremia in acute stages and also

the steroid pulse therapy is recommended and other therapy is chosen such as high-dose gammaglobulin or cyclosporin A or AT supplement therapy and plasma exchange is selected. However, most of the cases are used on the steroid pulse therapy at the mortality rate was in the beginning. It was 30 percent. But it's now decreasing down at 15 percent and nowadays ten percent is the mortality rate. Next one please.

This is the outcome of influenza acute encephalopathy and in the beginning, the death number was -- death rate was 30 percent and recovery was 45 percent and sequelae 25 percent, but it now changed. The death was ten percent and sequelae for 25 percent and the recovered case has now increased. Next one please.

And also we would be very welcome if the information comes to us. So this is the chief investigator, Dr. Morishima's, email address and myself the email address is listed

here. So if you have find any cases, please contact us or we are very happy to share the information about it. Next one please.

This is recent progress or recent change to influenza in Japan and one is influenza immunization and as you know, our country immunized to many of the school children for the influenza vaccine the first time. But this policy has been changed from the young generation to the senior population and now maybe around 70 percent of the elderly people are now receiving the influenza immunization every year. Next one please.

And the next topic is introducing of the rapid diagnosis kits in clinics. It is very popular and most of the doctors like to use to confirm the diagnosis and the next one. The next slide please.

And a choice of the antiviral drugs in the practitioners level -- and the introducing of anti-influenza drugs in clinics and accepted very widely. The next one.

So this is the outcome of the Tamiflu prescription by year in Japan indicated in this color. In 2001, it is introduced in the world and there is no difference, no big difference, between other countries and Japan. But from 2002, 2003 and 2005, most of the Tamiflu are used or has been used in my country. Maybe 70 to 80 percent of the production is consumed in my country. But people are very happy to feel the easy to decrease time of the fever and they are very comfortable to accept these drugs. The next one please.

But this is a presentation of abnormal behavior with Tamiflu in 2005 and 2006 in the Japanese Pediatric Infectious Disease Society annual meeting. Dr. Hama reported ten cases of abnormal behaviors. So the sources of the information on him is a review of the papers and also the personal information and five cases sudden death during sleeping after taking Tamiflu and two cases of

accidental death associated with abnormal behavior after taking Tamiflu. The three cases of sudden death after taking Tamiflu but no information about the sleeping on these cases. And also Dr. Hoshino also reported two cases of abnormal behavior after taking Tamiflu. The next year, this doctor, Dr. Hama et al., reported 15 cases including all these ten cases delirium without Tamiflu or, excuse me, 15 delirium without Tamiflu group and 52 cases including these cases with Tamiflu and he presented that the delirium was observed higher among Tamiflu but low fever groups and odds ratio was 44. Next one please.

And then the Minister of Health and Welfare collected the information and also joined with the pharmaceutical companies as an adverse events and up to May 31, 2007, this year, total 1,377 patients reported and 567 cases reported as neuropsychiatric event cases and 211 cases showed symptoms like abnormal behaviors. Twenty cases led to falling or

jumping off high buildings and six of them were fatal, and 71 fatal cases including 12 sudden deaths. This is reported from the clinician through pharmaceutical companies and more cases are being reported and scrutinized as of today. Next one please.

This is Dr. Goto, a pediatrician, presented in the Japanese Pediatric Journal on the experiences on abnormal behavior divided by two groups. This group's abnormal behavior appeared before receiving the Tamiflu and this groups showing abnormal behavior appeared after receiving Tamiflu. This number zero, 12, 24, 36 indicate hours after onset of fever. So the triangle indicates fever and taking Tamiflu this time, this time, this time and so on and abnormal behavior occurred before using of the Tamiflu, these groups, and the other group abnormal behavior showed after receiving Tamiflu, case number two, case number three, case number four and case number five, nine here and ten and 12 and 13. So

this is very random with Tamiflu or without Tamiflu occurring of the abnormal behaviors. Next slide please.

And this is the time from receiving Tamiflu to onset of abnormal behavior. Zero hours mean they are taking Tamiflu and, for example, in ten hours after taking the Tamiflu, the abnormal behavior occurred. So this is also very random. The blue color indicates the boys group and the red color indicates the girls group. Also this is another pediatrician made a report in a pediatric journal in Japan. Next one please.

And this is the latest one, a report from Japan Pediatric Society, Commonlaw Branch group, presented of Japanese Pediatric Infectious Society annual meeting. It was held two or three weeks ago in November 2007 and they collect 130 cases from the 12 hospitals and 38 clinics. The 05/06 season, the total number was 12, and 06/07 season total number was, I think, 130. They were

divided for the A, B, C, D, groups. The group A abnormal behavior possible to progress to accident or to hurt to others, total number please look for your paper and it is, excuse me, 22 cases here and B shows illusion, abnormal sense of vision, abnormal talk and, excuse me; the B group, illusion, abnormal sense and visions, this is 42 cases. The C group here, talk in delusion, sing song something, meaningless motion, etc. appeared on 36 cases. And D group scared, angry, cried or expressionless, the report number was 17. Next one please.

This is abnormal behavior with or without Tamiflu. This color indicates Tamiflu group and the red color indicates without Tamiflu group and group A, group B, group C, group D indicates of some abnormal behaviors for Tamiflu and this is for the acetaminophen. This is also a very popular drugs to use for the children febrile diseases in Japan and also the blue color indicates acetaminophen

plus group and the red color acetaminophen minus group and there is no statistical meaning. So there is no big difference between the Tamiflu group and the non-Tamiflu group and also the acetaminophen group. A little bit higher in acetaminophen group, but statistically this is no difference. Next one please.

And also the age and six distribution on abnormal behavior groups, so one year, this is one year and two years, three years, four, five, six, seven year and ten, 14 and 16 age groups and the blue color indicates for boys and the red color indicates for girls groups. The mean age is higher in school age groups and particularly in the boy group. So this is abnormal behavior associated with the influenza not related for some drugs. Next one please.

This is the conclusion of the report from Kanagawa Pediatric Group. One hundred thirty cases of abnormal behavior were

reported from pediatric clinics and hospitals in the Kanagawa Prefecture and almost two times higher in boys and higher in elementary school age groups than infant age groups especially in severe case group, school age and boys were higher and no differences were observed among influenza virus type with or without Tamiflu group and with or without acetaminophen groups. And this factor could not be a contribute for serious abnormal behaviors. But this is also the report from the Kanagawa Pediatric Group and we are now emphasizing that it is necessary to do more data about it. Next one please.

An issue to be tackled by this flu season, scrutinize closely the cases of abnormal behavior and sudden death and psychiatrists and subcommittee suggested, the subcommittee means the Ministry of Health and the Labor and Welfare Organized Research Group on Epidemiology and Clinical and Psychiatric Group and also the Virological groups. And

the psychiatrists in the subcommittee suggested that the similarity to the sleep disorders of abnormal behavior reported in teenagers and also additional studies to be conducted. It is now ongoing, sleep laboratory study and non clinical study and epidemiological studies. Next one please.

Epidemiological studies, it was done on a 05/06 season related for the influenza encephalopathy. Professor Shumpei Yokota, he is also one of the members of Influenza Encephalopathy Research Group and he did some epidemiological studies. The title is "Scientific Study on The Current Status of Influenza-Associated Symptoms" and the study method prepared of a questionnaire, a survey sheet, distributed them to pediatricians in 05/06 influenza season.

This is the result. It was already over, but this is not the final result. In 2,800 pediatric patients, 19.4 percent of them were less than ten years old and there was no

significant difference between Tamiflu unused and used groups for occurrence frequency of abnormal behavior, etc., where the frequencies were 10.6 percent in unused against 11.9 percent in the used group. About 90 percent of abnormal behavior and other clinical symptoms expressed on the first day and the second days of the illness. Next one please.

And on 06/07, improvement of epidemiological study on 05/06 will be done and the chief investigator is moved from Dr. Yokota to Professor Doctor Yoshio Hirota. He is a epidemiologist but very famous on influenza epidemiology in Japan and the survey scale with be up to ten thousand cases. The scope of the subjects is age, enhancement of a research scope to target influenza patients in teenager group. A more precise examination on the time relationship between observed symptoms and the drug use, but this is ongoing and they are now -- I mean the Professor Hirota group is now analyzing the data and it

will be appear within this year. Next one please.

Also the National Survey for Influenza-Associated Abnormal Behaviors will be done because actually we don't have any background data what is the frequence or what about the case number and what is the severity of some abnormal behavior associated with seasonal influenza without or with use with some drugs. And the chief investigator is myself and the study title is "National Survey for Influenza-Associated Abnormal Behaviors."

And the study purpose here is to grasp the number of abnormal behaviors and the details by gathering case reports from medical institutes and divided for two parts. One is the survey for serious cases and we call for all doctors in Japan to report the data. The data collection of the cases where the patient have been diagnosed as influenza and shows serious abnormal behaviors. Serious abnormal behaviors are the acts which might lead to

fatal endings such as jumping off high buildings or running abruptly.

Data collection term, the last and next flu season, we are now collecting the last season's data and nearly 130 cases reported. But around 50/50 at the moment. But it will be also open within the year in detail about these data.

The next one is the survey for non serious cases and we call for the influenza sentinels because maybe this number is higher than the serious cases and data collection of the cases where the patient has been diagnosed as influenza and show non serious abnormal behaviors. Non serious abnormal behaviors are the acts which might not lead to fatal cases such as flapping the hands, with a scared to something, etc. And data collection terms is this influenza season and just recently it has been started. Next one please.

So this is all of my presentation. So some slides are difficult to recognize.

I'm very sorry. But I'm very happy to respond if you have any questions. But please use the easy English and the slow speaking please. Thank you very much.

(Applause.)

CHAIRPERSON RAPPLEY: Thank you very much, Dr. Okabe, for traveling to be with us today and presenting this in person. I'd like to open the floor up for clarifying questions. If you signal me, we'll try to keep you in order. Yes.

DR. BIER: Do you have data on how many children in Japan jump off buildings during the non flu season? Do we have other control data on that?

DR. OKABE: Yes. In the past season, this is very difficult. Actually, we have the cases of the jumping out from the high building, etc., or suicide cases. But there is no data that the victims were associated with influenza or not influenza. But recently, recently means the last season,

that kind of action is very -- Well, an interesting point in the social. So some jumping over the young generation has influenza and without Tamiflu we have these cases and also there are some cases jumping over with influenza taking other antiviral agents, etc. But that is just report. So there is no epidemiological data. That is the reason we wanted to start the abnormal behavior surveillance associated with the influenza.

CHAIRPERSON RAPPLEY: Dr. Hall.

DR. HALL: Thank you and Domo Arigato gozai mashita.

DR. OKABE: Thank you very much.

DR. HALL: Very impressive and we appreciate it. I have two questions. First of all, the slide 33 that you have there talks about the timing of when they got the Tamiflu and although there are only a few cases reported here, these were all the children that had fever and then got Tamiflu, it looks

as if they were getting abnormal responses after Tamiflu that it occurred after the first dose and I don't see among these few that there was any that got it only after a second or third. Some then got it recurrently. My question really is on all of the children or on more children do you have that same information. Is that true that if it were to occur it occurred after the first dose of Tamiflu and then if it occurred subsequently?

My second question would be about your vaccination for children currently and whether this is influenced, the percent, that get immunized each year.

DR. OKABE: In regard for the first question, before the inflammation comes widely, the Tamiflu is used in many children and the dose also prescribed of the Tamiflu and make the decision to use continuously if it is decreased down on the fever and five days, this is total use of the Tamiflu date. So that is why if the patient occurred some

mild abnormal behaviors the parents are used. That is why the second attack was found. Recently this kind of the information is provided for all of the doctors so they are now discontinued to stop to use if some of abnormality occurs.

And with regards for the vaccination, most of the recommendation in the senior groups more than 65 years old in Japan but also the young generation including the infant group is willing to receive the influenza immunization, but I think 30 to 40 percent is a coverage of the children group nowadays. Thirty to 40, 3-0 to 4-0 percent. Not reached for the 50 percent.

DR. HALL: Were these children immunized?

DR. OKABE: Yes. Excuse me. This is divided for two groups.

DR. HALL: Right.

DR. OKABE: So mostly half and half and some children received the vaccine and 10

to 15 days of the first shot they suffered, he or she suffered, by the influenza. So this is very difficult to differentiate it for the natural infection or adverse events of the infant's immunization. So this is alos still being discussed.

DR. HALL: Thank you.

CHAIRPERSON RAPPLEY: Dr. Cnaan.

DR. CNAAN: I guess I'm still trying to understand the numbers and what you've just said. Thirty to 40 percent of children received Tamiflu or of children who received -- who have influenza -- What is 30 or 40 percent of what?

DR. OKABE: So the national level or the whole level the investigation is not done for their coverage of the Tamiflu of the children with influenza. But according to some research group, particularly practitioners/pediatricians, 60 to 70 percent of the patients of influenza has received the Tamiflu.

DR. CNAAN: Okay.

DR. OKABE: In the children's group.

DR. CNAAN: Now is it also given prophylactically to a large degree without influenza?

DR. OKABE: Prophylactic use is your question?

DR. CNAAN: Yes. Is Tamiflu given to a lot of people prophylactically without influenza?

DR. OKABE: Prophylactic use is allowed as a choice with the pharmaceutical law. However, it is very limited for the very specific patient, for example, the high risk group or the take caring group for the senior age groups. So I could say the prophylactic using is not so popular.

DR. CNAAN: Okay. And one more question. You have all of these events, the neuropsychiatric events, from your sentinel sites. Can you calculate because you know the

patient base in the sentinel sites the rates of the events? I mean, I think for once we have the denominator. Is that not true?

DR. OKABE: Yes. So this is very difficult, but maybe the denominator is used for the present situation of the seasonal influenza. But actually, the doctor -- Well, data collected just for the sentinels. So it is difficult to say the correct number and around 10 to 20 percent of the total number could be captured by the sentinel reporting system for the total influenza.

CHAIRPERSON RAPPLEY: Okay. We have Dr. Gorman next, then Havens, Ward and Daum.

DR. GORMAN: On one of your slides, you showed data for acetaminophen use besides Tamiflu. Do you have any information on any other drug these people were taking?

DR. OKABE: For the influenza, yes, this is very difficult to analyze. But normally besides antiviral drugs, the

acetaminophen for the fever and also the antihistamine drugs and anti-cough drugs as well. So this is very popular area drugs.

DR. GORMAN: The question was mainly directed at the gender preference for boys being two to one. Do you have any information on mental health drugs being taken by these individuals?

DR. OKABE: No, I don't have any information. So this is also the information that the febrile convulsion is very higher in our population. Almost ten percent of the children had an experience of febrile convulsion. I think it is higher than the coefficient groups. And also regarding with the febrile convulsion also it is mainly higher.

CHAIRPERSON RAPPLEY: Dr. Havens.

DR. HAVENS: Thank you very much for a really great presentation. A lot of complex data. It seems like there are two types of cases that you've presented, one in

younger people with influenza acute encephalopathy cytokine storm and longer duration of disease that might have shown up in the CDC case definition that we heard about earlier.

The neuropsychiatric event type case that you identify in the second part of your presentation is in an older age group without cytokine storm and I think importantly seems to be occurring in the first two days of influenza symptoms when oseltamivir would also have been given early in the disease course.

The question is what's the duration of symptoms of these people who you've identified with neuropsychiatric events. Some of the cases that we see in the material that we were given suggests that there's really a range of symptom duration from short to recurrent and potentially longer. Do you have information on the duration of symptoms of the people who presented with neuropsychiatric events?

DR. OKABE: Yes. So that is a point and that is a reason that we would like to collect the information from the patient, the duration and also the timing of the onset of psychiatric abnormal behaviors and at the moment there is very random about the information and this is very difficult to analyze in this stage and also this abnormal behavior will be related for the sleeping status. So it is the amount of sleeping or after the waking up stage or not related for their sleeping. So this is also, I think, one of the factors that should be collected, the information.

But so far, I'm sorry, I don't have any talk in detail. And also regarding the first term, my feeling is the encephalopathy and also these kind of the abnormal behavior associated with influenza is something different and influenza encephalopathy is one of the pathological changing in a general situation and also it is very serious.

According to our data, this kind of abnormal behavior groups do not progress to the influenza encephalopathy. Most of them stopped as the abnormal behavior situation.

DR. HAVENS: Thank you very much.

CHAIRPERSON RAPPLEY: Dr. Ward.

DR. WARD: I, too, thank you for bringing a great deal of data to us. I'm trying to sort out in my own mind the difference between host response and the infection and whether you have any information about if somebody has one of these neuropsychiatric events one year whether they're more likely to have it in a subsequent influenza outbreak and whether if they are monozygotic twins whether they are likely to both exhibit this cytokine reaction to the influenza infection.

DR. OKABE: The normal influenza or febrile convulsion and also influenza encephalopathy, my colleague has already presented the data of the cytokine situation

and the amount of influenza encephalopathy particularly if it's higher. But we don't have any data of the abnormal behavior groups on the cytokine level and also the other cytokine symptom groups at the moment. But also it should be the point to investigate it.

CHAIRPERSON RAPPLEY: Dr. Daum.

DR. DAUM: So my question goes to something that almost passed by and I think might be interesting. You talked about prophylactic use of oseltamivir. Do you see neurologic events in people using it prophylactically and have you looked for them and would that be a fertile way to sort of explore drug use in the absence of influenza?

DR. OKABE: As I talked, the prophylactic using of the Tamiflu for influenza is very small numbers. So we don't have any information about it if something happened associated as using of the prophylactic using. We don't have any data about it.

DR. DAUM: But for what it's worth, so no data at all.

DR. OKABE: No data.

DR. DAUM: I mean, nobody jumps off buildings who takes prophylactic.

DR. OKABE: Yes, because nobody in the pediatric group we don't use the prophylactic using.

DR. DAUM: Okay.

DR. OKABE: So you mean if the prophylactic using is done some abnormal behavior occurred or not. Yes, we don't have any data.

CHAIRPERSON RAPPLEY: Dr. Rosenthal.

DR. ROSENTHAL: Actually, Dr. Daum just channeled my question.

CHAIRPERSON RAPPLEY: Dr. Newman.

DR. NEWMAN: My question has been answered, too. Thanks.

CHAIRPERSON RAPPLEY: Other questions? Yes.

DR. McMAHON: This question is about the slide entitled "Outcome of IAE." I had noticed and I thought it was very interesting that the decrease in mortality had occurred over the last five years and I was wondering if you have sort of granular data on the predictors of decreased mortality.

DR. OKABE: I'm sorry. I could not catch.

DR. NEWMAN: I was wondering if you have information about what in the IAE group is predicting the decrease in mortality.

DR. OKABE: One of the factors is to understand about the inference of the knowledge of the influenza encephalopathy. So the merging room in pediatrician is everybody knows about the inference in encephalopathy associated with influenza and if it is serious to transfer to the more intensive care group, transfer to their patient, and also regarding for the treatment and most of them are receiving the high dose of the steroid. I

think that is one of the factors to improving of mortality rate. But not only for the treatment of the steroid therapy, but also the other supportive therapy has now progressed for these encephalopathy patients.

Is it good for your answer?

DR. McMAHON: Yes. I wouldn't imagine that you would have any control data in this population. There are various different ways of performing therapy.

DR. OKABE: There are quite a few numbers but we have the comparative data with the high dose steroid group and also without high dose the plus therapy group and clearly the prognosis is better in high dose therapy group. If you wish to see that data, later on I will show you the slide. Maybe I have.

CHAIRPERSON RAPPLEY: Dr. Hall.

DR. HALL: Thank you again. My question again about -- This is going toward pathogenesis which was part of whether they were immunized and why maybe it was in post

immune reaction responding to steroids or other aspects. This though is looking at the question of whether it is the agent itself meaning, first of all, do you see it with other drugs which was partially asked, but particularly zanamivir as other neuraminidase inhibitors? I don't know if you have enough cases that do receive that or, secondly, the viral agent, taking another virus that is similar which may not be as evident in terms of having a sharp peak. But if that virus such as a parainfluenza virus or a respiratory syncytial virus, if you see similar cases occur.

DR. OKABE: So with regarding for the antiviral drugs, they mainly use oseltamivir. So we have less information about other drugs such as zanamivir or etc. or amantadine also. But actually the abnormal behavior or influenza encephalopathy some patients were used to other antiviral drugs.

And also the second question for --

DR. HALL: The other --

DR. OKABE: For other viral agents, yes.

DR. HALL: Right.

DR. OKABE: The influenza is just one disease for such as a big curve. So during the influenza season we have many patients of the influenza, no, acute encephalopathy. But some patients is associated with RS virus infection as you indicated or herpes and others and also in the summer season AV71 is one of the agents. However, these are the very small number and they are not such big cases, such a number, as the influenza. So the similar cases is yes. We have similar acute encephalopathy associated with other ARI infectious agents. However their number is treated different.

CHAIRPERSON RAPPLEY: Dr. Lewis.

DR. LEWIS: Yes, I just had a followup question about the treatment for acute encephalitis associated with influenza.

You mentioned the pulse steroids as becoming pretty much the standard of treatment in Japan. Is that in addition to antiviral therapy usually or has it replaced antiviral therapy?

DR. OKABE: Yes, antiviral therapy it is later timing to use of the antivirals among, for the stage of acute encephalopathy. Also in the CNS definitely it is very rare to find out of the influenza virus. So it is not so useful to antiviral drugs among the, for the influenza patients.

However, the other research group recommended two choices of antiviral drugs for the patient of influenza encephalopathy because it may be possible to reduce of the total virological load from patient. So that might be some benefit. But there is no evidence about it.

DR. LEWIS: Thank you.

CHAIRPERSON RAPPLEY: Diane.

DR. MURPHY: Dr. Okabe, I have a

question for you and then I'm going to ask our ID people a question. But I'm going to come back to the suicide and I know this is not your area of expertise. But, in general, could you give us an idea for children who commit suicide in Japan, is there an age distribution, number one, that you know of? And, number two, when we look at how children commit suicide in this country, you know whether they -- we know that the girls tend to take medications versus the boys who shoot themselves or hang themselves? There tends to be a difference in the method. In the adolescents who commit suicide in Japan, do you know how they usually would do it? Would there be some other method than jumping or would that be a common method?

And then I'll come back to my next question.

DR. OKABE: This is not my field. So this is very hard to make an answer.

DR. MURPHY: I know.

DR. OKABE: So I will reply to you later to ask my friend or an expert please.

DR. MURPHY: Okay.

DR. OKABE: But actually insofar I know the suicide number in the young generation is now increasing rather than before very unfortunately and there are so many reasons.

DR. MURPHY: And there isn't a normal time of the year, but like after exams or anything that you know of that everybody knows or something like that? We'll just wait for you to get back to us.

My next question had to do with the slide which indicated that 40.8 percent of the virus was influenza B and is that pretty consistent? That's pretty high and I wanted to ask --

DR. OKABE: Yes. That's the last season.

DR. MURPHY: Just last season?

DR. OKABE: Yes.

DR. MURPHY: Okay.

DR. OKABE: So it depends on the season.

DR. MURPHY: Yes.

DR. OKABE: And also the distribution of the influenza virus is different in the United States or other European countries. It's here the change type to type. Some seasons it's very similar to the distribution with the Asian area or Western countries or the United States.

DR. MURPHY: So the 40 percent was unusually high then.

DR. OKABE: No, that depends.

DR. MURPHY: Okay.

DR. OKABE: Some seasons shows more than 50 -- It depends.

DR. MURPHY: To our ID people, how often would we see influenza B being 40 to 50 percent of the isolates? How frequently does that happen? Give us a perspective.

DR. HALL: Generally, it's not

common. But again, it's just as in Japan. It occurs at certain periods of time. It used to be about every five years, but that's no longer true and you can see small proportions almost every year or every other year. Last year we did see more influenza B than we had seen in the previous two seasons and I know what it was at home and it was close to 30 to 40 percent. I don't know nationwide. But we do this population based surveillance system and by that it was high for that year and often you can tell from the year before because you'll get a few trailings as maybe the third type that comes in at the end of the influenza season predicting what would be prominent the next year.

CHAIRPERSON RAPPLEY: We have three more people with questions and we're about ten minutes over. So if we continue, it will come out of our lunch time. Do people want to pose their questions or shall we -- What's the will of the Committee?

DR. MURPHY: I would like to suggest since he came all the way from Japan that we should eat quickly.

CHAIRPERSON RAPPLEY: Okay. That sounds good. Next then would be Dr. Cnaan.

DR. CNAAN: I have just one question about this graph of time from onset to abnormal behavior. You have here six where the abnormal behavior was before the Tamiflu and eight that it was after. What I didn't understand is who are these 14 children because 14 is no number that appeared in any of the previous slides. Are they a random selection? Who are they?

DR. OKABE: That is not a random selection. That experience is for one of the hospital data, one of the data.

DR. CNAAN: One hospital?

DR. OKABE: One hospital, yes.

DR. CNAAN: That you got the data.

DR. OKABE: Yes.

DR. CNAAN: Okay. That's all.

Thank you.

CHAIRPERSON RAPPLEY: Dr. Kimberlin.

DR. KIMBERLIN: What dose of Tamiflu is typically used in Japan in pediatric patients? Is it based as it is in the United States or is it a milligram per kilogram dose?

DR. OKABE: Yes. I think dose is the same.

DR. KIMBERLIN: Same as in the U.S.?

DR. OKABE: Yes.

DR. KIMBERLIN: And can you comment on use of oseltamivir in children under a year of age in Japan?

DR. OKABE: Yes, that's also in discussion and the pharmaceutical companies do not recommend to prescribe in very small children. However, some of the pediatricians are willing to use and they are doing the clinical trials for efficacy and also the

safety. But normally less than one year old is not recommended to use the Tamiflu.

CHAIRPERSON RAPPLEY: Dr. Newman.

DR. NEWMAN: Tom Newman. Again, thanks for coming. Mostly your presentation I think was reassuring especially the slide with comparing Tamiflu with acetaminophen. But one of your slides there was an odds ratio of 44 for Tamiflu use and delirium and possibly that was in a subgroup of low fever. Can you comment at all more on that study by Hama with the odds ratio of 44 how that got that high? Was that a very small subgroup? Do you know whether -- What the confidence interval for that was or just anymore about that odds ratio of 44?

DR. OKABE: Yes. So Dr. Hama collected the data from their website and also the information personally to come to the clinic. So that is why we want to open at the national level and the data collected from the sentinels and also we call all of the doctors

for the very serious ones.

DR. NEWMAN: Okay. So this was a website collecting cases where people who had used Tamiflu saw abnormal behavior. It sounds like a very biased way of collecting the data. That may account for it if they were.

DR. OKABE: My feeling is the data collecting bias will be.

DR. NEWMAN: Thank you.

CHAIRPERSON RAPPLEY: And we will have a letter that Dr. Hama has provided to the Committee and we'll read that at the public forum section.

Other questions?

(No verbal response.)

CHAIRPERSON RAPPLEY: And, Dr. Okabe, will you be around in the afternoon with us?

DR. OKABE: Pardon?

CHAIRPERSON RAPPLEY: Will you be staying for the afternoon session with us?

DR. OKABE: Yes.

CHAIRPERSON RAPPLEY: So you'll be available for more questions I'm sure we will have.

DR. OKABE: Yes. I will have a very hard time, but I will be here.

CHAIRPERSON RAPPLEY: Thank you very much.

DR. OKABE: Thank you very much.

CHAIRPERSON RAPPLEY: Okay. So we'll take a break, a ten minute break, and we'll be back at, maybe less than ten minutes, let's be back at twenty minutes to the hour. Thank you. Off the record.

(Whereupon, at 10:31 a.m., the above-entitled matter recessed and reconvened at 10:43 a.m.)

CHAIRPERSON RAPPLEY: We are going to revise the agenda just a little bit. We'll have the presentation from Dr. Lewis, and then from Dr. Rothstein, and instead of taking questions at that point, we'll break for lunch. We'll resume again at 1:00 for the

open hearing, and take the clarification questions for Dr. Lewis and Dr. Rothstein after the public hearing, and be back on regular schedule at 2:00 p.m. with our presentation from Roche.

DR. LEWIS: Thank you. My name is Linda Lewis. I am the Medical Reviewer for Tamiflu in the Division of Antiviral Products at the FDA, and I have to say this is the third time I've stood before this Committee to discuss these events, and I hope that today we can come to a better conclusion than we have come to in the last couple of years.

Because I know there are a number of people on this committee who were not present in 2005 when we did our last full evaluation of these events with presentations, at that time from the CDC and Roche, I would like to go over some of the things that happened in earlier meetings. Next slide, please.

So first, I'd like to give you just

a brief regulatory history of Tamiflu. Then I'll give recaps for both the 2005 original advisory committee, which was part of the Best Pharmaceuticals for Children Act mandated reporting. 2006 was really an update for the Pediatric Advisory Committee, and then I'll summarize some of the new data that we've been looking at since our last meeting and report to the Committee this year. Next.

Tamiflu was approved for use in the treatment of uncomplicated influenza in adult patients and, unfortunately, in adults means 13 years or older in this case, in October of 1999. In November of 2000, it was approved for prophylaxis in that same age group, and that included post exposure prophylaxis in a household setting, and also seasonal outbreak prophylaxis.

In December of 2002, Tamiflu was approved for the treatment of influenza in pediatric patients greater than one year of age. In March of 2004, Tamiflu and Roche were

granted pediatric exclusivity on the basis of the pediatric clinical trials, and some preclinical animal toxicity data that was available at that time. And lastly, just after the original Pediatric Advisory Committee, in December of 2005, Tamiflu was approved for post exposure prophylaxis in patients greater than one year of age. Next slide.

The next few slides will be a recap of our original BPCA Pediatric Safety Review. Next slide.

At that time in 2005, the Office of Surveillance and Epidemiology reviewed our adverse event reporting system database for pediatric adverse event cases during the one year period following Tamiflu pediatric exclusivity. This is mandated by the Best Pharmaceuticals for Children Act, and covered the period from March of 2004 to April of 2005.

In addition, they evaluated a

cumulative total of deaths in pediatric patients, and found 12 deaths since the time of Tamiflu initial approval. At that time, all of the deaths were reported from patients in Japan. During that review, they identified 75 pediatric adverse event cases in the database that covered the review period and, of these cases, 69 were originating from Japan, five from the U.S., and one from Canada.

The most concerning events identified in that original review were the neuropsychiatric adverse events, and serious skin reactions. The serious skin reactions were thought to be highly unlikely to be related to direct influenza infection, but are certainly noted to be very rare events with many drugs that are on the market today. Next slide.

At that time, we conducted a reanalysis of all of the clinical trials data in pediatric studies for Tamiflu. We had two

large treatment trials in children, and in those treatment trials, there was one neuropsychiatric adverse event reported. This happened to be in a nine-year-old male with confirmed influenza B who was hospitalized with a diagnosis of viral encephalitis. This patient happened to have received placebo in that clinical trial.

We had one prophylaxis trial that included pediatric patients, and in that study, there were two adolescents who were reported as having psychiatric events. An 18-year-old male with a described psychological disorder that was not further described, but was noted to have been present for one month prior to study entry. That patient had received Tamiflu for prophylaxis. There was also a 17-year-old female with a "nervous breakdown" that was not further described and a stated history of depression. This patient was hospitalized, but received no further treatment, and was therefore reported as a

serious adverse event because of the hospitalization. That patient had received Tamiflu as an index case in a household prophylaxis study. Next slide.

At that time, we also reviewed the pediatric literature for events of influenza-associated encephalitis and encephalopathy. At that time, it was quite clear that there were increased reports of influenza-associated encephalitis and encephalopathy that were originating from Japan that had been in the literature since the mid 1990s. This had apparently prompted nationwide surveillance efforts in Japan, as you've heard from Dr. Okabe, and both the medical community and the public were educated on the occurrence of central nervous system adverse events and complications of pneumonia. The Japanese reported continued high rates of influenza encephalitis and encephalopathy compared to U.S. and European populations, but it appeared in 2005 that mortality rates had decreased,

and I think this was confirmed in Dr. Okabe's presentation earlier.

There was some suggestion in the literature that the decreased mortality was due to both increased awareness of the complications, rapid diagnosis and treatment of influenza, and the institution of a treatment regime that he described that included both steroids and antiviral therapy. Next slide.

At that time as we were doing our review, the Division of Antiviral Products and the Office of Surveillance and Epidemiology requested additional information from the Japanese regulatory authorities, and from Roche, the sponsor of Tamiflu, regarding these neuropsychiatric events. At that time, it was not possible for us to get a representative from the Japanese regulatory authority to come to our advisory committee, but Roche did make a presentation, and described a number of their ongoing surveillance efforts.

We knew that the Japanese had undertaken active surveillance of influenza-associated encephalitis and encephalopathy beginning in the late 1990s. We were also able to determine that the Japanese National Health Service facilitated rapid diagnostic testing for influenza in children, and encouraged subsequent treatment.

We learned from Roche, through its Japanese pharmaceutical affiliate, Chugai, that they had solicited adverse event reporting, according to Japanese regulations, from approximately 70,000 Japanese physicians and clinics during the 2003-2004 flu season. So there was clearly enhanced reporting at that time based on what are considered the usual Japanese reporting regulations. Next slide.

At that time, the FDA had several conclusions regarding our adverse event reports. We knew that a search of the AERS database for this BPCA review covering the

year March `04 to April `05 had identified an unusual pattern of neuropsychiatric events, serious skin reactions, and a cumulative total of 12 pediatric deaths reported with Tamiflu use in pediatric patients.

However, a reanalysis of the pediatric clinical trials data failed to identify differences in skin or neuropsychiatric adverse events between children receiving Tamiflu and either placebo or no treatment in controlled clinical trials. It must be remembered that these clinical trials involved relatively small numbers of patients compared to those who have now received Tamiflu commercially. But they did enroll several hundred patients in those studies. Next slide.

We felt that there was further investigation into possible reasons for this pattern of adverse events in Japanese children. We knew there was a syndrome of influenza-associated encephalitis and

encephalopathy that had been described in the pediatric literature, and these had occurred prior to the approval of Tamiflu. We knew that there was increased awareness of these complications in Japan, and therefore increased used of diagnostic testing and treatment, particularly the use of Tamiflu, in children diagnosed with influenza in Japan. And we knew that there were probably increased levels of adverse event reporting during our review period. Next slide.

At that time, the FDA planned several actions. The Division of Antiviral Products in the Office of Surveillance and Epidemiology enacted monthly monitoring of adverse events reported with the use of Tamiflu and all of the other influenza antiviral drugs during every flu season. This adverse event information was shared with the CDC so that we could identify any trends, and try to match those to that particular flu season and epidemiology.

At that time, we planned no change in the Tamiflu labeling related to either pediatric deaths or neuropsychiatric adverse events, but we did feel that an update of the general pediatric safety and the severe skin reactions needed to go into the label at the time that we had our review of the pediatric post exposure prophylaxis indication. And we also committed at that time to come back to the PAC and report on continued adverse event monitoring. Next slide.

At that time, the Advisory Committee, as you always do, have many suggestions, and while they agreed with our general approach, they requested that both we and Roche might obtain some additional information. They asked if there could be information from Roche regarding analysis of AEs during Tamiflu prophylaxis compared to treatment. These questions had already come up in some of our earlier discussions.

The Advisory Committee asked if

there could be an estimate of incidence rates of the neuropsychiatric AEs, and I think that's come up this morning already also. There was also great interest in any additional pharmacokinetic, pharmacogenomic drug metabolism, or effects of CNS inflammation, and any data available that might pertain to or illuminate some of these events.

Information regarding adverse events gleaned from reviews of large healthcare databases was suggested, and we really hoped to have information regarding the natural history of influenza, complications of influenza, and management of influenza in pediatric patients in Japan, which we have now so nicely heard from Dr. Okabe. Next slide.

Now I'll give an even briefer update on last year's Advisory Committee. I think there are several members of the Committee who were here last year when this was done. Next slide.

We continued to review the AE reports monthly through the 2005-2006 flu season. At that time, we planned to do a brief update after the flu season, and not really intended as a full reevaluation as we had presented in 2005. At that time, the Office of Surveillance and Epidemiology developed categories for these neuropsychiatric adverse events that were clinically descriptive, not specifically MedDRA terms from the medical dictionary or any of the other regulatory descriptions. These were to aid in our understanding of these events and our review. You'll hear more about that categorization in the presentation just after mine.

In 2006 - next slide please - the OSE review identified 129 AERS case reports, and these were from all ages, during the year following our first report. Twenty-six of those reports were excluded because there was either too little information contained in the

report, or there were obvious medication errors that were involved, or they were confounded by concurrent medical and psychiatric disorders, making the reports uninterpretable.

We were left with 103 cases included in that review, and again, they were predominantly from Japan: 95 from Japan, five from the U.S., and three from other countries. The median age was 12 years, with a range from 1.5 to 90, and there were three cases that involved prophylactic use.

The Office of Surveillance and Epidemiology - sorry, next slide - identified these neuropsychiatric events as I said into eight categories that were more clinically descriptive, and these included -- the first number is the total number of cases in that category and, in parentheses, the number of U.S. cases. So the major category identified at that time was what we called "delirium with prominent behavioral disturbances," which

included a total of 60 cases. There were six events categorized as suicidal events, three categorized as panic attack, three as delusions, 12 as convulsions, six depressed level of consciousness, four with loss of consciousness, and nine that fit into miscellaneous categories like insomnia and night terrors, other things that didn't really fit into any one category. Next slide.

The characteristics of these reports and the follow-up review added more uncertainty that the events really represented a disease or influenza-only process. There were many factors that figured into that. There was a temporal association with the first one or two doses of Tamiflu and the event. In many cases, there was a stated drug effect as per the reporting physician. In some cases, there was a lack of sequelae after dechallenge, although this was somewhat difficult to determine from the types of reports we had.

There was clearly an absence of frank influenza encephalitis symptoms in most of the case reports, and what we had predominantly was a very unusual, and what I would describe as stereotypical pattern, described in many cases as just abnormal behavior, to these adverse event reports. These reports when you read them, and I've been reading these for the last three years, are really very similar. If you read them in, you know, a stack of them, they all start to sound alike.

There was concern that, if the U.S. drug use for Tamiflu increased, and became closer to the level of use that is current in Japan, we might well see increasing numbers of these adverse events if they were drug related. Next slide.

Again, the FDA had several planned actions in 2006. At that time, we were still uncertain regarding the etiology of these neuropsychiatric events, but we believed that

the number and pattern of events warranted some precautionary labeling. We felt that it was important to advise parents to closely monitor their children who were taking Tamiflu, or who had influenza, to prevent any unsafe behavior, and again, we promised to come back to the Advisory Committee this year with a more complete report, and with additional presentations from Roche and, if possible, the Japanese authorities, which we were able to accomplish. You'll be hearing from both Roche and Glaxo SmithKline a little later in the presentation.

The action that we took - next slide - the action that we took in 2006, which actually preceded the Advisory Committee by a short time, was to add new wording to the precaution section of the Tamiflu label, and I've just listed the exact wording of that on this slide. It is not very specific, and that was by intention. And we were also careful to say that we did not know the relative

contribution of Tamiflu to these events, but that patients should be closely monitored throughout a treatment period. Next slide.

So here we are, for the third time, and those of you who have been at previous advisory committees are probably wondering what we have now. Next slide.

So where are we now? At this time, the Office of Surveillance and Epidemiology has completed a full reevaluation of our AERS database for neuropsychiatric adverse events reported for all of the influenza antiviral drugs. In doing this, they've refined their descriptive categories for use in the reviews so that they would be similar for each drug product, and you'll get a more thorough description of that in the next talk. We've done an updated search of the pediatric scientific literature for both influenza-related events and drug-related events, and we've had more intensive discussions with our Japanese colleagues, and know that, as Dr.

Okabe pointed out, they have many ongoing clinical and laboratory studies in Japan, including national surveys, studies intended to evaluate sleep patterns, and others. Next slide.

We also know that Roche has conducted an extensive evaluation of these events, and they'll be presenting some of their information later. They are going to be presenting, I believe, their attempts to investigate the neuropsychiatric events through health claims databases. They've been looking through these databases and other sources to try and evaluate cases that might be related to prophylaxis, because that has been recurring question, and what I can say, and I think our drug safety reviewer will agree, is that it's almost impossible to pick out, of the kinds of reporting databases we have, cases that are reported with prophylaxis. In many cases, that just isn't in the report at all and, quite honestly,

there is not very much prophylactic use of Tamiflu in children, even in the United States, although probably more than in Japan, because we do have a number of immuno-compromised patients who receive Tamiflu in addition to vaccines since they might not be responsive to vaccine.

Roche has also conducted a number of scientific evaluations of possible mechanisms of neurologic events. Next slide.

So what I'm going to go through are some of the things that have turned up in our re-review of the scientific literature. Newland, et al., at the Children's Hospital of Philadelphia, recently published an article in the *Journal of Pediatrics* that included a four-year retrospective review of influenza-related neurologic complications in patients who had confirmed influenza. They identified 842 pediatric patients during this four-year review, and in that number, identified 72 patients with influenza-related neurologic

complications. They identified these patients by looking through their -- by first going through their laboratory database, and identifying confirmed cases of influenza, and then taking that set of patients and looking for evidence of either lumbar puncture, CNS imaging, a diagnosis of seizures, or other neurologic complications on discharge or admission notes, those things, and then reviewed those charts in detail.

Of the 72 patients they identified with neurologic complications of influenza, they identified eight with encephalopathy, two that they thought had a post infectious encephalopathy related to influenza. Seizures were identified in 56, and other neurologic manifestations in six. In their series, patients with encephalopathy generally had symptoms that began within three days of the respiratory symptoms, and included disorientation, lethargy, visual hallucinations, and speech abnormalities.

They identified the post infectious encephalopathy as somewhat similar symptoms, but occurring more than six days after the onset of fever.

They estimated that the incidence of neurologic complications using a population-based neighborhood cohort was somewhere in the neighborhood of 4.1 cases per 100,000 child years in their pediatric population in Philadelphia.

Shortly after that report came out, next slide, there was a follow-up report of similar events reported from the University of Hong Kong. Those investigators conducted a five-year review, and identified 874 patients with confirmed influenza. Of those, 182 patients were identified with neurologic complications, and in their series, febrile seizure accounted for over 90 percent of the neurologic complications, so 165 of 182 patients. They found encephalopathy in five patients, and encephalitis in one. They

estimated the incidence of neurologic complication in their population as around 240 per 100,000 person years, although their methods of estimating rates were not described very well in this brief article.

This is quite a bit higher than the estimates from the Philadelphia group, and the authors of this report speculated that it was partly attributable to the lower threshold for admission for influenza-related illness and febrile seizures in their Hong Kong population. Next slide.

We also looked at a newly published comparison of Tamiflu pharmacokinetic profiles in Japanese and Caucasian adults. This study evaluated two different doses of Tamiflu, and took pharmacokinetic sampling on days one and day seven of BID dosing. It was clear that the Caucasian subjects were taller, heavier, and had a higher BMI than the Japanese subjects. I suppose that's not too surprising. What they found was a slightly

increased C_{max} among the Japanese on day one, but that was not replicated on day seven. No other pharmacokinetic parameters were different, and the authors concluded that there was no clinically significant differences in PK parameters for oseltamivir or its metabolite, oseltamivir carboxylate. Next slide.

There have been a number of new hypotheses regarding potential etiologies of these neuropsychiatric adverse events, and they are primarily targeted at the Asian population. A Chinese group of researchers identified a nonsynonymous, single nucleotide polymorphism in human cytosolic sialidase that was in increased prevalence among Asians. Human sialidase is considered a homologue to neuraminidase, and there was a feeling that, since oseltamivir binds tightly to neuraminidase, it might also bind to human sialidase.

In this, they modeled the activity

and binding of oseltamivir to this unusual sialidase with single nucleotide polymorphism, and identified that it would result in increased binding affinity, and reduce sialidase activity. They speculated that this reduced sialidase activity, particularly in the face of Tamiflu, might lead to neuropsychiatric symptoms. They used as their comparison patients who have sialidase deficiency syndromes, which is a rare glycoprotein accumulation syndrome that does have prominent neurologic findings. Those findings, however, are not really similar to the types of abnormal behaviors that we have been seeing in our case reports.

Also, another group looked at the potential for oseltamivir to increase neuronal neuroexcitatory action using a number of different techniques. What they found was that, in mice who were given intraperitoneal Tamiflu, there were no particular notable changes in behavior.

However, when Tamiflu was given prior to the dose of ethanol, they identified increased ethanol-induced sedation, and lowered body temperature in rats. They also found that oseltamivir facilitated and increased some of their measures of neuronal excitation in rat hippocampal specimens. And they suggest that the effects of ethanol or other nervous system stimulants in combination with Tamiflu may lead to some behavioral changes.

Lastly, another group looked at levels of P-glycoprotein activity in the brain to see whether oseltamivir might accumulate if P-glycoprotein activity were either enhanced or diminished, and what they found was that low levels of P-glycoprotein activity might lead to accumulation of oseltamivir in the brain, and might therefore account for neuropsychiatric events. Next slide.

So in summary, we've identified the neuropsychiatric adverse events reported with

Tamiflu, and with other influenza drugs, continued to come into our reporting system. Over the years, we've noticed that there have been an increased number of neuropsychiatric adverse events reported each year since 2005. Now we have to remember that we've also had increased publicity about these events every November since 2005, and that's right before the influenza season. So hopefully we are raising awareness.

It remains difficult to separate the symptoms of influenza and the symptoms of possible drug reactions. And what we've found in the past year or so with a lot of intensive research is multiple hypotheses regarding the etiology of these events, or things that might be contributing factors. I would remind you, though, that all of these possible etiologies are highly speculative, and none of them have actually been linked to the patients who have the events. So they remain interesting theories, but with unknown clinical relevance

at this time.

I'll stop here and take questions.

CHAIRPERSON RAPPLEY: I think we'll hold the questions until after our open hearing. Thank you.

Dr. Adrienne Rothstein is going to present for us next. Dr. Rothstein is Safety Evaluator Division of the Drug Risk Evaluation, Office of Surveillance and Epidemiology.

DR. ROTHSTEIN: Good afternoon. Before I begin, I would like to acknowledge my colleagues who have contributed multiple analyses to this presentation. They would include Melissa Truffa, Evalyne Edwards, Kathy Dormitzer.

This is an overview of what I will be discussing today. I'll describe the adverse event reporting system. I'll provide an update on Tamiflu, including recent drug use data, and a comprehensive summary of deaths in pediatric patients, and a cumulative

summary of neuropsychiatric events, including a review of some health claims data. In addition, I will summarize the post marketing reports of neuropsychiatric events for the three other antiviral products currently marketed for the treatment and prophylaxis of influenza, which are zanamivir, amantadine, and rimantadine. I will provide our conclusions from our look at the post marketing data, and our recommendations in regards to these four products.

AERS is the acronym for the FDA's adverse event reporting system database, which is a repository of reported adverse drug reactions since 1969. It was formerly called the spontaneous reporting system, and has evolved over the years, including the addition of the MedDRA dictionary, which is the medical dictionary for regulatory activities, and it now accommodates electronic submissions. It contains over three million reports related to drug products and therapeutic biologics, and

more than 300,000 reports are received each year.

Reports related to vaccines are housed in the VAERS system, which is the Vaccine Adverse Event Reporting System, which is a joint program between the FDA and the CDC.

The AERS database has several strengths. Notably, it includes all U.S. marketed products, both drugs and therapeutic biologics. It is relatively simple and an inexpensive system. It may allow for the detection of events not seen in clinical trials. We may be able to identify safety signals when the product is used in a larger or different patient population than those enrolled in clinical trials.

These post marketing adverse events in this database, we can potentially identify events that are rare, or occur shortly after drug exposure, and from reviewing these reports, we construct case series to identify

trends in the reports, such as in regards to dosages, off-label use, or subpopulations, and any other significant information for the safety of the product.

The main limitations of a spontaneous reporting system is that there is gross under-reporting, reporting biases do exist, and the data do not provide either a numerator or a denominator. In terms of under-reporting, it has been estimated that only a small proportion of adverse drug reactions are ever reported to regulatory authorities.

It is well-known that reporting may be biased for a variety of reasons. For instance, severe reactions and unlabeled reactions are more likely to be reported than non-serious or labeled events. And publicity can also drive reporting, as well, and spontaneously reported data should not be used to determine the incidence of adverse events. Some of these limitations will be

particularly relevant when I discuss amantadine later.

Another limitation is related to the quality of information in the reports, which is often variable and incomplete. In this review, the Japanese reports are translated, which may make it difficult to understand the case narrative, and code the events in the adverse event coding dictionary. We also come across duplicate reports, and sometimes it can be difficult to attribute events with a high background rate, or confounders, such as disease or other medications, or a long time from the initial drug exposure to the event occurrence. However, despite these limitations, spontaneous reporting is the mainstay of early risk recognition.

As Dr. Lewis mentioned, there is enhanced monitoring of the influenza products. On a monthly basis during the influenza season, the Office of Surveillance and

Epidemiology tabulates and individually reviews the new post marketing adverse event reports for the four antiviral products, namely oseltamivir, zanamivir, amantadine and rimantadine, and then OSC prepares a monthly summary of these reports for the influenza products, and then OSC and the Division of Antiviral Products meet monthly during the influenza season to discuss these reports and identify any new safety signals.

If a new safety signal is identified, or a change in reporting of the labeled serious adverse event is identified, then OSC conducts a formal review of the AERS reports for that safety signal. We also look at prescription use data from the U.S. to identify any trends of interest, such as pediatric use.

Now I'll provide an update on oseltamivir, specifically in regards to drug use, pediatric reports for the fatal outcome, and a comprehensive summary of

neuropsychiatric events.

And this is a brief background on oseltamivir. It's a neurominidase inhibitor for the treatment and prophylaxis of influenza in patients one year of age or older. It was initially approved in October of 1999, and was granted pediatric exclusivity in March of 2004.

This is an excerpt of the current U.S. labeling, which was updated in November 2006, and I think this has previously been described, but it's just the precaution statements as there have been post marketing reports, mostly from Japan, of self-injury and delirium in influenza patients using oseltamivir. These reports were primarily among pediatric patients. The relative contribution to drug is unknown, and patients should be closely monitored for signs of abnormal behavior during the treatment period.

The next is the information from the Japanese package insert, which was updated

March of 2007 following the death of two more adolescents in Japan. The entire warning is listed for the Committee, but I would like to focus your attention to the statement about patients ages 10 to 19 years old.

Due to the reports of abnormal behavior of an unknown causal relationship, patients age 10 to 19 should refrain from using Tamiflu in principle, excluding those patients at high risk. The Japanese labeling mention that patients and family should be well informed about two things: the potential for developing abnormal behavior, and then also not to leave a child or teenage patient alone for at least two days.

And the next slide is information from the European label, and it also mentions abnormal behavior, hallucinations and delirium, and that accidental injury has rarely resulted from delirium, mainly in children and adolescents. It does state that these psychiatric symptoms have been reported

in influenza patients not taking oseltamivir.

There is also a package leaflet for patients, which also mentions a close monitoring of patients, especially children and adolescents, and it recommends contacting a health care professional immediately if the patient shows any signs of any unusual behavior.

And then I will provide some drug use information from our sources, and also from the sponsor. This slide shows the total number of oseltamivir prescriptions in the U.S. broken down by flu season. Note that the scale is in thousands. As you can see, the total number of oseltamivir prescriptions has decreased from almost two million in the `05-`06 flu season to 1.8 million in the last flu season.

However, use in pediatric patients is increasing, which is shown in light blue, which accounted for 28 percent of total prescriptions in the `05-`06 flu season, and

44 percent in the last flu season. We would like to point out, however, that we are unable to determine how much of this usage is for influenza prophylaxis.

The next slide is courtesy of the Tamiflu sponsor, Hoffmann-La Roche. It shows oseltamivir prescriptions by season and country, and this scale is in millions. As you can see, the prescriptions for oseltamivir in Japan, which is shown in blue, has decreased from a high of about nine million in the `04-`05 flu season, to about five million in the last flu season. As previously mentioned, usage in the U.S. decreased slightly from the last flu season, from the `05-`06 flu season, to the last flu season, and that is shown in red.

And this slide is a subset, which is pediatric patients, which here is defined as less than 16 years of age, and it also shows worldwide usage, which was provided by the sponsor, and the use of oseltamivir in

pediatric patients in Japan has decreased from a high of about 4.5 million in the `02-`03 flu season, to about 2.5 million in the `06-`07 flu season, and it shows a slight increase as well in the U.S. in pediatric patients in the last flu season.

The first set of post marketing data for oseltamivir that I will present is a cumulative summary of the pediatric death reports from U.S. approval in October of 1999 through May 31, 2007, and for the review of these fatalities and all the neuropsychiatric events, a pediatric patient is defined here as 21 years of age or younger.

As of May 31, there were 25 reports in the AERS database in pediatric patients that had a fatal outcome, which included 17 males and eight females. The majority of reports came from Japan, which was 21 cases: three from the U.S., and one from Egypt. Since the last Pediatric Advisory Committee update, we had received seven new reports,

which included two more reports from Japan of fatal traumatic injuries, and here is the breakdown of the 25 reports. There were five deaths from traumatic injuries, which were only reported in Japanese patients. I'll describe those briefly in the next slide. There were nine reports of sudden death, also from Japan, two deaths due to complications of influenza from the U.S., two reports of cardiopulmonary arrest, both were from Japan, and then one report each of Avian flu, acute pancreatitis, pneumonia, asphyxiation, possible encephalitis or cardiomyopathy, sepsis, and then finally the last report, which was also from the U.S., is an unspecified death months after receiving oseltamivir.

This slides summarizes the five deaths from traumatic injuries in Japanese pediatric patients. The first case occurred in February of 2004 in a 17 year old male who took one dose of oseltamivir, and then leapt

in front of a truck. He had also received amantadine, which was also considered a suspect drug in this case.

Then in February of 2005, a 14 year old male fell off the ninth floor of his building after one dose of oseltamivir. In July of 2006, a 12 year old male took one dose of oseltamivir, and was found lying in the parking lot of his building, presumably due to a fall. And then in February of 2007, two more reports of deaths due to traumatic injuries were received, both from Japan. A 14 year old male took two doses of Tamiflu, and told his mother he was going to the restroom, but instead opened the front door. He then jumped over a fence, and leapt from his 11th floor apartment, and a 14 year old female took one dose of oseltamivir. The mother had left the patient alone, and within three hours, she apparently fell from the tenth floor of her building.

This is our conclusions in regards

to the pediatric deaths. Based on the available data, it is still difficult to establish a direct causal relationship between the use of oseltamivir and the reported deaths because of comorbidity and confounding factors such as influenza in many of the cases. Issues with the translated reports and our limited access to follow-up information makes interpreting these foreign reports quite challenging. However, the contribution of oseltamivir and some of these deaths, especially the fatal reports from traumatic injuries, cannot be completely excluded at this time.

The second set of post marketing data that I will summarize are the reports of neuropsychiatric events for oseltamivir and, as Dr. Lewis mentioned, we were requested to do a complete review of all of these reports.

So the AERS database was searched for all reports from U.S. approval through May 31, 2007. Specific adverse event reports were

retrieved using MedDRA, which is the Medical Dictionary for Regulatory Activities. We used 51 high level terms that were previously agreed upon with the sponsor to identify these abnormal behaviors, and other events of concern. Also, we did an additional search for the HLT visual disturbances, because we identified that some visual hallucinations were reported under this HLT.

We were looking for reports where oseltamivir was listed as a suspect drug by the reporter. We had no restrictions on age, and then following the retrieval of these reports, we did a manual review of each case narrative, and then the case categories were assigned. These case categories will be described in more detail just shortly.

Using the search criteria that were described, we retrieved 728 reports from the AERS database. We excluded 132 reports. Similar to the last review, there were reports where the narrative did not support. It was

confounded by a medical or a psychiatric disorder that made the reports uninterpretable. So we were left with 596 cases in the review. Seventy-five percent of them were from Japan, 22 percent were from the U.S., and there were 22 from other geographies, Canada, Germany, France and Great Britain.

The median age for the patients in these cases was 14 years, with a range of three months to 94 years. There were slightly more males than females, with 335 males, and 247 females in these cases. The time to onset was a median of 24 hours. We also looked at number of doses reported, and it was one or two doses in 61 percent of the cases where the number of doses was specified.

The time to resolution in these cases was a median of six hours, and when we looked at the subset of pediatric patients, the time to resolution was three hours. It was very short. The indication for use, there

were 529 cases that reported treatment. In 200 cases, it was for treatment of type A influenza. In 99 cases, it was treatment of type B influenza. There were 19 prophylaxis cases, and the remaining 48, the indication for use was unknown.

I just want to describe the prophylaxis cases, which I know is of interest to the Committee. There was one report of delirium in a 17 year old U.S. male. He was confused after four days of oseltamivir. He wasn't sleeping, and his symptoms progressed to psychosis and paranoia, with auditory and visual hallucinations. This patient was hospitalized, and a urine drug screen was positive for marijuana and benzodiazepines.

There is also one report of a suicide attempt in a 49 year old patient following a night of drinking alcohol. Oseltamivir was initiated one week earlier. The patient was also receiving zolpidem.

Seizures were reported in eight

patients, and there were two patients each with a depressed level of consciousness or loss of consciousness, and there were five patients that fell into the miscellaneous category, which was three reports of confusion, one report of improved behavior, and one report of irritability and disorientation.

In summary, we feel there are no convincing cases of delirium or self-injury with the use of oseltamivir for flu prophylaxis in the AERS database.

This slide shows the nine categories that we specifically developed to summarize these neuropsychiatric events. These categories are a refinement of the categories used from the last review. This was a manual process. Every narrative was reviewed, and a category was assigned, sometimes following review by a panel of DDRE staff.

Most of the nine categories listed

on the slide are self-explanatory, but I want to describe a few of them in detail. The first category, DIB, is delirium with impulsive or injurious behavior. These were patients who had delirium or exhibited impulsive or injurious behaviors, such as jumping out of a window, grabbing a knife. These were cases where the patient's behavior harmed themself or a family member, or they were about to harm themselves and had to be forcefully stopped, such a parent holding a child back from jumping out of a window.

The second category, abbreviated DEL, is any report of delirium, delusions, hallucinations or psychosis. In these reports, there was no mention of a behavior that could directly lead to injury. Some examples in this category would be there was a patient who was hallucinating that he was planting rice in a field, and was acting out this hallucination. Another patient was putting salt and pepper on a compact disc and

was attempting to eat it. Another child saw a giant Pokeman sleeping next to him in bed. Again, the patient's behavior did not put them at risk for injury.

The third category is suicidal events, and for this, patients either threatened or attempted suicide, and the intent suicide was explicit, either a note or spoken words. Reports of patients found dead from traumatic injuries from a fall were not classified as a suicide unless there was explicit intent. There was one report of a patient who jumped from a hospital room, but he left a note. So we had to have explicit intent to be classified as those.

And then the category abbreviated as DLC is depressed level of consciousness, and that covers the spectrum of lethargy to coma, and the miscellaneous category was anything that didn't fall into these other eight categories, which was mostly insomnia and night terrors.

And then this is a summary of all 596 cases by the categories. The first one we've listed in order of relevance is delirium with the injurious behavior. Again, the abbreviation DIB. There were 48 pediatric cases, a total of 59, but the majority were in pediatric patients.

The next category of interest are the delirium and hallucination cases. There were a total of 225 cases. The majority of these occurred in pediatric patients with 176 cases.

And suicidal events, there were 12 events of suicide attempts or ideation. The bulk of these were in adults.

And the miscellaneous category here unfortunately ended up with quite a few, but the most commonly reported were insomnia in 23 reports, abnormal behavior not otherwise specified, nine reports. There were eight reports of night terror. There is reports of unusual speech or agitation or confusion, with

five reports each, etc. So it's just anything that fell out.

There were a few cases where the patients had two distinct categories of events, and the decision that would be delusions and seizures, seizures and depressed level of consciousness. The decision was made to capture both categories, because these were distinct and significant categories, and we didn't want to lose that.

We did examine how many cases had fever, and found that 30 percent of the cases documented a fever at event onset. This was higher in pediatric cases with about 41 percent documenting a fever. However, in about half of all cases, it was unknown if a fever was happening at the time of the event, again, one of the limitations of post marketed data.

This slide shows the neuropsychiatric events for only the pediatric patients, and we broke it down into age groups

of zero to 12 years, and 13 to 21 years, just to get a sense of how old the patients were. There were a total of, as we mentioned, 48 cases of delirium with injurious behavior. In brackets, you can see that three cases occurred in the U.S.

Examples of these typical cases will be shown later, and there was a total of 176 pediatric cases of delirium, delusions and hallucinations and psychosis without the injurious behavior, and the majority of these cases occurred in patients less than zero to 12 years of age.

And then the suicidal events, there were three in pediatric patients, one in the zero to 12 age group, and two in the 13 to 21 group.

What's interesting here in the miscellaneous group, the most common events shift a little bit. Insomnia is more common in adults, and in pediatric patients, night terrors were more common in this age group.

I wanted to summarize some of the U.S. reports of delirium with impulsive behavior and self injury. There was a 20-month-old male who's afraid of his mother, and he ran away from her. He was also banging his head against the wall to the point where it was said he should wear a helmet. He was in danger of injuring himself.

There was a 10-year-old male whose delirium was manifested as throwing lawn chairs off of a cruise ship and screaming. The patient also made a run for the cruise ship railing.

There was also a 14-year-old male, which I will get into in detail for the next page.

So this 14-year-old male in the U.S. received approximately two doses of oseltamivir for influenza. He woke up delirious, hallucinating, and ran to the window and tried to jump out. According to the father who reported it, he was acting

crazy and ranting and said "I'm going insane." The episode lasted about 15 minutes. The father contacted the pediatrician, and was advised to take the child to the emergency room, but he opted to stay home because the child was back to his normal self, and there was a heavy snowstorm outside. The pediatrician advised the father to sleep with the child in the same room, and lock all the windows and doors. The child did well overnight. The next morning he appeared well. He had no fever. He only had a mild cough and upper respiratory symptoms. Physical exam was unremarkable. Neurological exam was normal. Patient denied any ingestion of other medicines or substances. A comprehensive urine toxicology screen was negative for all substances.

And I wanted to give a sense of some of the reports that we're receiving from Japan. This is a report of a 13-year-old male. He took two doses of oseltamivir for

influenza. His mother was instructed not to leave him alone for 24 hours from the administration of oseltamivir. The patient went to bed that evening in his own bedroom. Five hours after going to sleep, he felt like he was having a dream where he was being chased, and then he felt something touch his feet. He found himself hanging from the edge of a third floor window with his feet on a 10 centimeter ledge. He climbed back up through the window, and went to his parents' bedroom and told them, "I was almost dead. I was terrified." The parents assumed he was dreaming, and he climbed into bed with them and they fell back to sleep.

The next morning, his mother noticed the scratches on his forearms and dirty feet. The mother went to his room and saw the open window and the footmarks on the ledge. Five hours later, he was afebrile, calm, and in good condition at the clinic. We -- the only temperature reported in this case

was when he received his last dose of oseltamivir at 8:00 p.m. We know that his temperature was 38 to 39 degrees.

The next case is concerning a nine-year-old female, and this occurred in March of 2007 in Japan. The patient took oseltamivir and went to bed. About 30 minutes later, she was heard crying out. When a family member went to see her, she was running to the veranda. The family tried to stop her by force, but she shouted, "I must go." The family took her to the bathroom by force where she shouted and threw objects. She settled down in about five minutes, seemingly regaining consciousness, and spoke normally.

On a visit to the hospital later, her consciousness was clear, and this case demonstrates a typical case where there's an abrupt onset, and the event rapidly resolves. And also, as was mentioned previously, these neuropsychiatric events occurred shortly after a patient awoke from sleep.

The next report is from the U.S. It's just a report of a delirium, but it's a compelling report from an adult patient, and this is only an excerpt of the narrative, but it clearly articulates what these events are like. She wrote, this 47-year-old female, and this is March of 2007, "I experienced a very disturbing neuropsychiatric side effect on the third day of using oseltamivir for the treatment of influenza A. I first experienced significant anxiety, and a strange sensation in my head upon taking the fourth dose of Tamiflu, and immediately alerted the prescribing healthcare provider, who suggested trying to get through one more day of treatment. After the next dose, I began to hallucinate, seeing swarms of insects outside the window and on the ceiling. I felt almost paralyzed in my bed. When I closed my eyes, I saw sprays of vivid color, and eventually had a very unsettling dream from which I awoke very abruptly two hours later.

I struggled to get out of bed to notify a family member to keep an eye on me. My condition improved throughout the night, but I decided to stop oseltamivir. I no longer had a fever, and was caught off guard with the reaction. There was no warning of this sort of side effect provided with the drug. I consider this reaction to be very serious, because I have four children and my husband was out of town. It was bad enough to be sick with the flu, but to be delusional was considerably worse and dangerous.

I would have appreciated a warning or a caution before taking the drug, and possibly a recommendation to discontinue the medication at the first sign of neuropsychiatric symptoms. The results could have been disastrous."

That's the last of the reports from the AERS database that I was going to present, and now we're going to discuss the last source of post marketing data for this review, which

is the health claims databases, and this was reviewed by an epidemiologist in my division. These were retrospective cohort studies, primarily evaluating influenza-related mortality, and the complications of pneumonia and myocardial infarction.

Two sets of analyses were performed, and Roche has provided a report of their own analyses of both datasets. The two databases that were used were the MarketScan Database was the first one, which is compromised of beneficiaries of employer-sponsored health plans and Medicare, and the UnitedHealthCare Database, which contains data from patients insured by UHC, and from large national employer groups with administrative services provided by UHC, cases where patients who had a outpatient claim for an influenza diagnosis at an outpatient visit, and a prescription for oseltamivir within one day of diagnosis, and met the inclusion criteria.

The control group was selected from

a pool of patients who had an influenza claim, and did not have a claim for an oseltamivir prescription or any other antiviral medication.

The market scan data examined a number of different outcomes that included rates of pneumonia, otitis media, and other respiratory conditions, as well as related hospitalizations. Selected cardiovascular or neuropsychiatric events were also examined, but were not stratified by age. The adult sample size for market scan was greater than 73,000, and the pediatric population was greater than 25,000, and pediatric here was defined as ages 12 or under.

UnitedHealthCare also examined cardiovascular outcomes, and neuropsychiatric events, but was not stratified by age. At the FDA's request, a second analysis was performed where the outcomes were stratified into patients aged zero to 17 years, and 18 years and older. There were greater than 100,000

pediatric subjects, and greater than 140,000 adults.

The health claims studies reported numerous outcomes, and the FDA is just reporting on the pertinent outcomes that were not null findings, and were clinically meaningful. For the MarketScan database, they had the following notable outcomes. Among the pediatric population, as compared with patients that did not receive an antiviral therapy, patients receiving oseltamivir were 55 percent less likely to have a physician visit claim for pneumonia than non-antiviral users in the 30 days following an influenza diagnosis. They were also almost 70 percent less likely to have a physician visit claim for a respiratory ailment, and 74 percent less likely to have a physician visit claim for otitis media.

Roche conducted its own analysis of the UnitedHealthCare data using Ingenix's data, and found that patients under 17 years

of age receiving oseltamivir were 41 percent less likely to have a visit for encephalitis than patients that did not receive antivirals. Ingenix also examined the neuropsychiatric events for the UnitedHealthCare data, and they also stratified their findings by age group. They found that patients under 18 years of age receiving oseltamivir were 1.69 times more likely to have a physician visit for affective psychosis than patients who had not received antivirals.

There are some strengths of using the health claims database to look for these neuropsychiatric events. First of all, there are large robust datasets, and at our request, the second round of analyses did stratify the results by the appropriate age groups, and information was provided on how the psychiatric outcomes were defined, and they reported on events that occurred within 14 days of the influenza diagnosis.

Some of the challenges to using

these data are that neuropsychiatric events may not be fully captured using health claims data. The small number of events makes it difficult to achieve statistical significance. There is uncertain validity of the neuropsychiatric event diagnoses, and there's a lack of information on possible unmeasured confounders.

Although the previous Pediatric Advisory Committee recommended that Roche examine health claims data, it's important to keep in mind that, given the difficulty of capturing these idiosyncratic neuropsychiatric events, such as the ones recorded in AERS, it may not be fully recorded in the health claims data.

So our conclusions in regards to the neuropsychiatric events with oseltamivir is that we continue to receive reports of abnormal behavior. There are still no compelling cases of abnormal behavior with prophylaxis. However, since the last update,

there are now U.S. reports of these abnormal behavior with impulsive injurious behavior, and these events continue to have an abrupt onset and rapid resolution. Some of these events have occurred, even with adult supervision. But it is still difficult to definitively determine if these events are due to drug, disease, or both.

Next I will discuss the other antivirals used for influenza, the zanamivir, amantadine, and rimantadine. I will provide some drug use information for these products to put it in perspective.

This slide, as you can see in red, is Flumadine, zanamivir is shown in yellow, and then the light green is amantadine. And this is data across the last five flu seasons, and the scale on this is in thousands. Because of recent shifts in influenza strain susceptibility patterns, the CDC has warned healthcare providers against using rimantadine and amantadine during the last two influenza

seasons, which is why you see a steep drop off there. And then, however, usage for these products is much, much less than oseltamivir in the U.S.

And the first of the other antivirals that I will describe in detail is zanamivir. Just a brief background as well on this product, it's a neurominidase inhibitor in the same therapeutic class as oseltamivir. It is available as an oral inhalation powder with systemic absorption of approximately only four to 17 percent of the inhaled dose. The sponsor is Glaxo SmithKline, and its indications in the U.S. are treatment of influenza in patients seven years of age or older, and prophylaxis of influenza in patients five years of age or older. It was approved around the same time as oseltamivir, and it was approved in July of 1999. And the neuropsychiatric events listed on the U.S. label are seizures and syncope.

It's a similar review method of the

AERS database. The data was retrieved from the date of U.S. approval through August 1, 2007. The 51 HLTs, and they're available as an appendix at the end of the review, those were searched looking for Zanamivir as either a suspect or concomitant medication, no restrictions on age group, and again, we applied, after a manual review of these reports, we applied these case categories.

The search retrieved 166 AERS reports. Fifty-one reports were excluded. Mainly the narrative did not support, or the cases were confounded by concurrent medical or psychiatric disorder. So that left us with a total of 115 cases in the review. Seventy percent of the cases came from Japan, and about 25 percent of the cases came from the U.S. The median age in this case series was 13 years, with a range of five to 79 years. Sixty-four percent of the reports occurred in patients 21 years of age or less.

The indications for use in this

case series, 109 of the cases involved treatment. Twenty-three reported type A influenza, and 20 reported type B. There were no prophylaxis cases, and indication for use was unknown in six cases. There was about an equal distribution between males and females, and the time to onset here was a median of about 12 hours, or one or two doses in 65 percent of cases, and the time to resolution was a median of 24 hours and, for zanamivir, fever was reported in about 50 percent of the pediatric cases.

Before I get into the actual cases, we just want to point out that, although zanamivir was approved around the same time as oseltamivir, the number of cases of neuropsychiatric events in the AERS database was very low initially until the last flu season. There was a large increase in reports of neuropsychiatric events in the `06-`07 flu season.

So this is a summary of all the 115

cases broken down by the categories. There was a total of seven reports of delirium with injurious behavior, including six pediatric patients, and there were 61 reports of delirium and hallucination. The bulk of them were in pediatric patients. These seven cases of delirium and injurious behavior will be described in more detail, and I also wanted to point out that, in contrast to oseltamivir, there have been no reports of suicidal events.

This next slide shows the pediatric cases by category, and depicting how many were in the U.S. There have been no reports in the U.S. of delirium with injurious behavior. However, there is one report of delirium in the U.S. in pediatric patients.

And just to give you a sense of these reports, these are excerpts from typical case narratives, which read very similar to oseltamivir. There's an abrupt onset after one or two doses, and then a rapid resolution of the events, and many of these reports

mention the patient had just woken up.

The first one is a five-year-old male from Japan. Five hours after the first dose of zanamivir for influenza, the patient developed abnormal behavior, hallucinations, difficulty speaking, and urinary incontinence. The patient uttered nonsensical phrases, and then the patient suddenly dashed to the entrance of the house, but did not get out. That abnormal behavior occurred again 30 minutes later, and the patient was absentminded, but came to himself within ten minutes. The head CT did not show any abnormalities, and the patient returned to normal the next day.

The second case shown here is an 11-year-old male, also from Japan. One hour after the first dose of zanamivir for influenza, the patient suddenly woke up and said, "I can't find the square thing. No, that isn't what I want." He stood up and tried to rush out from the room, and he said

things like, "That side is the dream. This side isn't. I want to go to the dream side." He started to cry out things such as, "What is the matter with my life?" and he was very afraid. He calmed down after about 15 minutes and told his mother, "I'm okay now."

So in summary for zanamivir, we had 115 cases of neuropsychiatric events, seven cases with this delirium and impulsive and injurious behavior. There were six cases in pediatric patients. There were no fatalities, and no U.S. cases for this impulsive and injurious behavior.

A relationship of these neuropsychiatric events to influenza is suggested by the low systemic absorption of the product. As previously mentioned, only four to 17 percent of zanamivir is systemically absorbed. Most of these events occurred shortly after the initiation of therapy, as I mentioned, one or two doses in 65 percent of cases, and at that time, fever

is likely.

And then in some cases, the patient continued receiving zanamivir, and the events did not recur with subsequent doses. However, a relationship to zanamivir is also suggested by the onset of the event occurring soon after the initiation of therapy, which implies a relationship to drug. The median time to onset was 12 hours, or one or two doses in 65 percent of cases, and also there were cases that supported a relationship to zanamivir, because the events recurred with each dose that a patient received.

Our conclusion is that, for zanamivir, the evidence favors an influenza-induced etiology, but we cannot rule out the possible contribution of drug.

And then looking at amantadine, amantadine is an older drug. It was approved in 1966. It is considered an M2 inhibitor antiviral, and it's approved for treatment and prophylaxis of influenza A in patients one

year of age or older, and the current U.S. labeling has extensive information about neuropsychiatric events, including a warning about suicide attempts, and an increase in seizures in patients with a history of epilepsy. Many of these patients have received a short course of amantadine for influenza treatment and prophylaxis. The warning also states that amantadine can exacerbate mental problems in patients with a history of psychiatric disorder, and patients may exhibit disorientation, agitation, aggressive behavior, hallucinations, paranoia.

But before I present the post marketing data that we retrieved from the AERS database, it's important to recall some of the limitations of spontaneous reporting. As I mentioned previously, there is gross under-reporting, and reporting biases exist, and cannot be used to estimate a numerator or a denominator. And we know that severe reactions and unlabeled reactions are more

likely to be reported than non-serious or labeled events. So one should be cautious about comparing several products, especially an older drug that is well labeled for CNS toxicity, to some of these newer drugs.

So these are our search criteria of the AERS database, approval through July 30, 2007. Again, we used the 51 HLTs. And the primary suspect drug here was amantadine, and we retrieved any age group, and did a manual review. Then we decided to focus on pediatric cases when we retrieved the cases, because amantadine is also used for Parkinsonism symptoms, and drug-induced extraparametal symptoms, and we wanted to see if there were similar neuropsychiatric events such as delirium with injurious behavior in pediatric patients using amantadine for influenza. So this was a subset analysis of the reports.

Eight hundred and forty reports were retrieved from the AERS database, and the review focused on 42 unduplicated pediatric

cases, 41 from the U.S., and one from Canada. The median age for these patients was 11 years, with a range of 2.5 to 20 years. The indication for use in these patients was treatment in 28 cases, prophylaxis in six, and in eight cases, the indication was unknown. It was about evenly split between males and females, and what's different from oseltamivir and zanamivir was the time to onset here was a median of five days, which is very different from what was previously presented.

For amantadine, there were no additional pediatric cases of delirium with injurious behavior identifying. As you may recall, I previously presented the one pediatric death of a 17-year-old who leapt in front of a truck following the use of oseltamivir and amantadine. That is not shown here, because it was previously discussed. But there were 18 pediatric cases of delirium or hallucinations and psychosis without this injurious behavior, and there were three

pediatric cases of suicidal events. Again, amantadine has a warning about suicidal events.

Our summary for amantadine is that CNS toxicity is known to occur with amantadine. There's a warning in the label. A subset of neuropsychiatric events, these 42 pediatric cases were reviewed. We didn't identify any additional cases of delirium with impulsive and self-injurious behavior in this subset analysis.

Due to the few numbers of reports of neuropsychiatric events in pediatric patients retrieved from the AERS database, we have limited ability to draw further conclusions. However, the absence of reports in the AERS database does not mean that events are not occurring. As mentioned earlier, gross under-reporting is a limitation of spontaneous reporting.

In summary, the current labeling for amantadine contains adequate information

on suicide attempts and CNS toxicities.

And the last antiviral that I will be discussing is rimantadine. Like amantadine, it is an M2 inhibitor antiviral. It was approved in September of 1993, and it has approval for treatment and prophylaxis of influenza A, and it's also approved for prophylaxis of influenza A in children. The precautions mention seizures, and the labeling also mentions impairment of concentration, agitation, some euphoria and hallucinations.

These are the search criteria for the AERS database, again, using the 51 HLTs, and we likewise focused on pediatric cases. There were 82 reports retrieved from the AERS database, and we focused on four unduplicated pediatric cases.

The indication for use in this group was three patients were using it for treatment, one for prophylaxis. The median age in this small case series was 14.5 with all of the cases occurring in males. There

was one report retrieved of delirious, injurious, impulsive behavior. A 13-year-old male developed hyperactivity. He wanted to light matches, and became psychotic four days after initiating rimantadine for influenza and, according to the reporter, a medical evaluation excluded a flu-induced encephalopathy. Because of this one case, a search was done to look in adult patients and see if there were similar reports. Fifty-two reports of neuropsychiatric events in adults were reviewed, but similar cases were not found.

And this is just the summary from the four cases reviewed for rimantadine. Again, there is one pediatric case of delirium with injurious and impulsive behavior, and then in addition, there is one report of delirium, and there were no suicidal events retrieved.

And the conclusions from the rimantadine review, there were four pediatric

cases of neuropsychiatric events reviewed. There was one case of delirium with impulsive and self-injurious behavior, and further review of adult reports didn't identify any more cases.

And these are the recommendations from the GDRE review that was completed. For oseltamivir, there's a recommendation from GDRE to update the U.S. label to provide some additional details to note that these cases in Japanese adults and children were fatal. The onset was abrupt, and events occurred even while patients were being monitored. However, as I described, there are some examples where patients successfully stopped the child before they hurt themselves, the U.S. case that I described where the father stopped his son from jumping out of the window, and then was advised by his pediatrician to stay in the same room with the son and lock the windows and doors.

We believe that no restrictions by

age seem warranted at this time in the U.S. because the causal relationship is still unclear. We are not sure if it's drug, disease, or the combination. But we ask to consider a further risk communication, like a public health advisory or a prescriber alert. The example I gave with the woman who was at home with her four children, she was unaware of the potential for these types of events.

We will continue enhanced monitoring of post marketed data, and we'll evaluate these events further if there is a significant change, and we await more data from Japan, as previously mentioned by my colleague, Dr. Okabe.

In regards to zanamivir, we think it is prudent at this time to caution prescribers and patients, because we are seeing very similar reports. We would like to add a precaution describing these post marketed reports of hallucinations, delirium and abnormal behavior in patients receiving

zanamivir for influenza treatment, and to include a statement about monitoring for signs of abnormal behavior throughout the treatment period, and we would continue this enhanced monitoring of the post marketing data.

In regards to amantadine and rimantadine, amantadine is well-known to cause CNS toxicity and suicide attempts. A limited look at the post marketing data did not identify any additional reports of this abnormal injurious behavior. We have no recommendations at this time. However, we would continue to closely monitor this post marketing data.

And I would like to acknowledge the contributions of my colleagues in getting this presentation together. Thank you.

CHAIRPERSON RAPPLEY: Thank you very much. I think we'll take our questions after our public hearing, and is anyone present at this point in time who will request to speak at the open public hearing?

(No verbal response.)

That being the case, is it permissible to resume at 1:15 p.m.?

DR. MURPHY: Yes. I think nobody is here. By law, what we publish in the Federal Register, we have to start the open public hearing at 1:00. But since we've only had one submission and nobody is here, we will start at 1:15 and hope that, if anybody shows up that they have a bit more flexibility than between 1:00 and 1:15. Thank you.

CHAIRPERSON RAPPLEY: Okay. Then we'll reconvene here then at 1:15 then. Thank you.

(Whereupon, at 12:10 p.m., the above-entitled matter recessed to reconvene at 1:12 p.m. the same day.)

CHAIRPERSON RAPPLEY: On the record. Again, I would like to ask if there is anyone who would like to speak during the public hearing.

(No response.)

CHAIRPERSON RAPPLEY: As I mentioned earlier, we do have a letter that I will read as part of the public hearing process and then after I read the letter we'll close the public hearing if there are no further presentations and we'll move to clarifying questions on our two previous presentations.

So this is in regard to the open public hearing. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the Advisory Committee Meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the Committee of any financial relationship you may have with the sponsors,

their products, if known, their direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The letter we have is addressed to Dr. Dianne Murphy, Dr. Ann McMahon, Dr. Catherine Dormitzer and Dr. Andrew Mosholder and it is from Dr. Rokuro Hama. He is Editor of the, and you'll have to forgive my pronunciation, `Kusuri-no-Check' which in English is Check Up Your Medicine, roughly translated, Deputy Editor of "The Informed Prescriber," Chairman of Japan Institute of

Pharmacovigilance, Invited Professor of Osaka University of Pharmaceutical Sciences.

He writes, "I noticed that the Pediatric Advisory Committee November 27-28, 2007 will discuss on the neuropsychiatric adverse reactions to Tamiflu. I would like to make some comments on this issue, because I am a physician who reported one sudden death case and two abnormal behavior cases both with fatal outcome related to Tamiflu at a scientific meeting in Japan in Nov. 2005 and I am very much concerned about the issue.

I would be very grateful if you and your committee would consider my comments that warn the potential harm of Tamiflu and the underlying mechanisms inducing not only sudden death and sudden onset of neuropsychiatric adverse reactions but also delayed onset with prolonged effects."

And his comments follow. "More than fifty sudden deaths must be taken into account in analyzing adverse reactions to Tamiflu.

Since Nov. 2005, I have been consulted with additional bereaved families, eight in total, whose children had severe adverse reactions to Tamiflu including those with sequelae or fatal outcomes.

You concluded, `However, the postmarketing data for oseltamivir continue to suggest a possible association between the use of oseltamivir and the development of neuropsychiatric events.' In general, your comments in the paper by Dr. Catherine Dormitzer and Dr. Andrew Mosholder seem to offer better analysis and conclusion of the causality of Tamiflu and abnormal behavior than that of Japanese Ministry of Health Labour and Welfare. However, I wonder why you do not discuss the sudden death after taking Tamifllu and the results of animal experiments this time. They are too important to be missed in discussion of the causality between the drug and its adverse reactions.

Memorandum by Evelyn T. Edwards and

Melissa M. Truffa issued August 24, 2005 reported that among 12 of pediatric fatal cases, at least five were sudden death, including additional four and three were death from acute cardiopulmonary arrest. They considered that `sudden death' as an unusual phenomenon in otherwise healthy pediatric patients with influenza and concluded `Although these reports do not allow us to assess causality of oseltamivir, the contribution of the drug to the death of these patients, especially with the cases of sudden death and cardiopulmonary arrest cannot be excluded based upon the information available.'

I wrote a letter to the British Medical Journal in July 2007 as follows;

On 16 June 2007, the Japanese Ministry of Health Labour and Welfare announced that by 31 May 2007 it had received 1,377 reports of adverse reactions since 2001, when marketing of oseltamivir started in

Japan. Of these, 567 were serious neuropsychiatric cases, 211 showing abnormal behavior. The number of deaths reported was 71. In addition to these 71 deaths, there were nine sudden deaths which the ministry did not recognize as adverse reactions. Of the total 80 deaths, 50 were sudden deaths or deaths from sudden cardiopulmonary arrest 18 in those less than 10 years old, 32 in those aged 20 or over, while eight were accidental deaths from abnormal behavior. five in teenagers, three in those aged 20 or over.

In addition, I have examined medical records of eight cases in total including autopsy reports if available: five died and three survived. Two died from accident after abnormal behavior presented at the scientific meeting. Three suddenly died during sleep, two infants and one adult.

I was very much surprised that the three-year-old boy," and he provides a case number for that, (#5758389A) was excluded

according to Appendix 4, List of Excluded Cases-Oseltamivir, because I analyzed his medical records and found he had no history of asthma and about two hours after taking only one dose of Tamiflu, he was found arrested by his mother. He had lung edema at autopsy which indicates that he suffered from severe hypoxia just before death. This finding, lung edema, coincides with the lung edema observed in 9 of 18 dead among twenty-four 7-day-old rats that were treated with only 20 times as much doses of oseltamivir as human dose based on the plasma concentration.

According to the autopsy results, a 39-year-old previously healthy male was suspected to die three hours after he took two capsules of Tamiflu as indicated by his doctor. He had also severe lung edema: the same findings as the boy and as unweaned rats.

This type of lung edema is frequently reported in the severe hypoxic conditions such as acute asphyxia, sleep apnea syndrome and

high-altitude disease.

A 14-year-old boy experienced agitation, cyanosis, conscious loss and seizure but recovered completely, while a 10-month-old girl had retrograde development and mental retardation after transient apparent recovery from the events with loss of consciousness and seizure.

Another type of neuropsychiatric adverse reaction was seen in a 15-year-old boy: delayed onset and prolonged neuropsychiatric adverse reactions after almost full dose of Tamiflu and they lasted for two weeks.

By overviewing 80 death cases including 50 sudden deaths and eight accidental deaths from abnormal behaviors, animal experiments and the latest laboratory findings, I classify adverse reactions to Tamiflu as follows:

1) Sudden onset adverse reactions typically after taking one or two doses of

Tamiflu which is related to central nervous system suppressant action of oseltamivir including sudden deaths during sleep or with respiratory suppression, sudden onset abnormal behaviors and other acute onset neuropsychiatric disorders with short duration.

2) Delayed onset adverse reactions occurring after taking several or full dose of Tamiflu probably caused by oseltamivir carboxylate, in other words, delayed onset neuropsychiatric reactions with prolonged duration, pneumonia, sepsis with multiorgan failure, bleeding and hyperglycemia.

3) Allergic reactions involving various organs and others.

Mechanisms of adverse reactions to oseltamivir and the causal relationship are summarized as follows:

(1) Unchanged oseltamivir has central nervous system suppressive action based on the similarity of signs, symptoms and pathological

findings to those of hypnotics and sedatives. Decreased body temperature, decreased spontaneous movements, slow/irregular breathing, cyanosis and lung edema. Especially pulmonary suppression and lung edema at autopsy or transient lung edema if survived, are important findings observed both in animals and in human sudden death cases or near fatal survived cases. Concentration of oseltamivir may be increased if potency of P-glycoprotein which is found to be a transporter of oseltamivir in brain recently, decreases when one has influenza. Binding capacity of unchanged oseltamivir to P-glycoprotein is also confirmed by other investigators including both that of the manufacturer of Tamiflu and independent to the manufacturer.

Severe sequelae may be related to the delayed neuronal damage following temporary cardiopulmonary arrest induced by oseltamivir.

(2) Abnormal behaviors, delirium,

hallucinations and even suicide could be the symptoms as the results of disinhibition or dyscontrol due to the CNS suppressant action of oseltamivir.

(3) Delayed onset reactions to Tamiflu may be related to its inhibitory action of oseltamivir carboxylate to sialidase, neuraminidase, a key enzyme for antiviral activity. Sialidase is also a key enzyme for wide variety of mammalian physiological processes. Administration of oseltamivir to people with certain type of single nucleotide polymorphism might further reduce their sialidase activity. Reduction of its activity may affects immune functions, cell apoptosis and glucose metabolites by influencing conformation of glycoproteins and gangliosides that are important component of cell structure and function and may play a role for maintaining normal potency of P-glycoprotein.

And it is signed, Rokuro Hama, M.D.

So once again, I will ask if anybody would like to present at our open public hearing.

(No response.)

CHAIRPERSON RAPPLEY: No takers on that opportunity. We will move to clarifying questions on the two previous presentations by Linda Lewis and Adrienne Rothstein.

Would anybody like to open with questions? Yes, Dr. Hall.

DR. HALL: I would like to ask about in the last presentation the -- it would be nice I guess I should say to have some relative understanding of the number of adverse events between, say, Tamiflu and zanamivir and we don't have necessarily a denominator, but I wondered if there was an analysis in terms of the number of prescriptions that were written as we saw with some of the Japanese and that would have had to be done by years. So, in other words, is zanamivir the same as with Tamiflu or would

the other drugs which are not as frequent obviously now?

DR. ROTHSTEIN: In our analysis, we did not calculate reporting rates to compare the products. There are many issues biases towards reporting and as I showed on the slide for zanamivir we only started receiving reports. The bulk of the reports came in the last flu season. But in total, there were 596 cases of these neuropsychiatric events for oseltamivir and 115 for zanamivir. But we did not calculate reporting rates. There definitely seem to -- potentially, all the media attention from Japan drove some of the reporting for zanamivir in the last flu season.

DR. LEWIS: Just one comment. I don't know if we can get the slides pulled up from Adrienne's presentation, but we did have global drug usage data from Japan and the U.S. compared to the rest of the world for both Tamiflu and for Relenza. We did not for the

other two drugs because it seemed less critical with the recent suggestions not to use those drugs for influenza.

But slide, I believe, it's 39 was the zanamivir usage.

DR. ROTHSTEIN: Yes. Thirty-nine.

DR. LEWIS: Do you know the Tamiflu?

DR. ROTHSTEIN: Tamiflu is -- that would be -- thirteen is Tamiflu in the U.S.

DR. LEWIS: So that gets sort of a yearly total of -- okay. That's the Tamiflu.

DR. ROTHSTEIN: In the U.S.

DR. LEWIS: That's just U.S. data.

DR. ROTHSTEIN: The next slide is worldwide.

DR. LEWIS: Yes. And that's the comparison, thank you, Japanese to U.S., Japanese in the blue in the range of millions of doses each flu season and in the U.S. about 1.5 to 2 million doses per year over the last three flu seasons and then slide 39, this is the similar accounting of the Relenza use in

yellow. This is just U.S. data. But as you can see, these are in hundreds of thousands.

DR. ROTHSTEIN: Thousands.

DR. LEWIS: Sorry, thousands. In thousands. So over the last few flu seasons compared to 1.5 to 2 million courses of Tamiflu, there have been seven or six thousand courses if I'm reading the table correctly of Relenza in the U.S. In Japan, there was higher usage and I believe that someone is going to show that data in one of the next presentations. But it is also higher than the U.S. usage. So relatively speaking, there is several fold more Tamiflu use than Relenza for numbers that are not that disparate from year to year for the last flu season.

DR. HALL: So are you saying then that the relative rate between Tamiflu and zanamivir at least for the U.S. would be approximately the same? I can't do that calculation.

DR. LEWIS: I'm not sure I can do

that calculation either and I'm not sure that the data we have really allow us to do that calculation based on the reporting and the types of drug usage data that we have.

DR. HALL: Thank you.

CHAIRPERSON RAPPLEY: Dr. Daum.

DR. DAUM: Thank you.

CHAIRPERSON RAPPLEY: Robert. Is it relevant to this? There were two other ahead of you.

DR. DAUM: I'm sorry. No. It's not relevant and I'm happy to wait in line. You just called on me and let's keep moving.

CHAIRPERSON RAPPLEY: Thank you. Dr. Cnaan.

DR. CNAAN: Actually, this is relevant to the previous question. You cannot get relative rates in the proper sense because of all of the reasons that you said. But what I think you can get is probably a valid comparison between the four. The absolute number will be meaningless, exactly like

you're saying. But if you take something like the market share of these four drugs and compare the numbers of reports and for all of the biases in the reports they shouldn't inherently be different from one drug to the other, all of the considerations of biases of not having denominators are true for all drugs. So comparing relative to market shares should be able to be done in some fashion.

DR. ROTHSTEIN: Let me pull up the slide with showing the zanamivir reporting over time. It's very different. If you would go to slide 44, we looked at the number of reports for flu season for oseltamivir and zanamivir and they were very different and there was a spike for the last flu season for zanamivir. So we didn't think it was appropriate to compare. We thought that this might represent stimulated reporting and we didn't think it was fair to compare.

And then broadening it out to all four drugs, amantadine has extensive labeling

about suicidal events and neuropsychiatric events. But our review of the database identified very few reports and it's an old drug that's been around since 1966. It's really -- you can't really compare across these products. That's why we did not choose -- People -- it's difficult. There are so many caveats to the data that it wouldn't really be meaningful to try and compare across these four products over time. Some were approved 40 years ago and it's really not meaningful.

We tried to look for these reports to just see are there similar narrative, do they have a similar onset and resolution and that's what we were looking at when we were comparing across the four products.

CHAIRPERSON RAPPLEY: Dr. Havens.

DR. LEWIS: What's --

CHAIRPERSON RAPPLEY: Sorry. Go ahead.

DR. LEWIS: Sorry. One thing that we

can say is we had really seen almost no activity with Relenza until this past flu season and this spike in reporting gave us a flu season with approximately the same number of adverse event reports as we reported to this Committee with the first Advisory Committee for Tamiflu. So it was very similar in character and quality and quantity to that first advisory committee in 2005 when we first started tracking oseltamivir cases.

CHAIRPERSON RAPPLEY: Dr. Havens.

DR. HAVENS: Thanks very much. I had a question on the last presentation slide 34, oseltamivir results on neuropsychiatric events from the health claims databases. The first part of that slide seemed to suggest that oseltamivir is good inasmuch as it decreases the direct complications you might associate with invasive influenza disease and its complications.

But the second part of the slide was on the UHC data. I don't understand the

difference in the analysis, the UHC reported by Roche versus the UHC data reported by Ingenix. Can you help me understand that because the way you guys have done the neuropsychiatric case definitions is very special and really clearly shows a pattern that might not be captured in using other definitions. Here it seems like you're showing different results depending on what you do with going from the basic data to a specific case definition and I don't understand how you got to the difference between encephalitis and effective psychosis.

DR. ROTHSTEIN: I'm going to have my colleague, Cathy Dormitzer, handle that. She's the epidemiologist that did this review. This is her area of specialty.

DR. DORMITZER: We did not conduct the analysis. We are simply reporting on the -- can you hear me? Okay. We're simply reporting on the results that the sponsor provided us and they were different analyses.

What UHC did was they did propensities for matching and used it in their analysis. What Roche did with their analysis was in order to select their sample they computed a propensity score and then selected their sample based on that. So it's slightly different.

Now the first thing I have to say though is with encephalitis, the numbers are very, very low. It was 17 and seven. So it's based on a very, very small number and the same thing is true for affective psychosis. The numbers are very small. So it's difficult to, I don't know, put a lot of weight on these estimates. At the same time, they were noteworthy. So I wouldn't put a lot of emphasis on these numbers, on these estimates.

CHAIRPERSON RAPPLEY: Did you understand part of that differences to be related to what we've discussed earlier that encephalitis is actually a different entity or different cluster of symptoms than is abnormal behavior which abnormal behavior might be

categorized as affective psychosis?

DR. DORMITZER: I would need someone from Roche to answer that question.

CHAIRPERSON RAPPLEY: Maybe we could ask when they give their presentation.

DR. DORMITZER: These are based on physician presentations. These are based on outpatient physicians claims in their health claims data set.

CHAIRPERSON RAPPLEY: Right. So I think that becomes an important distinction for us. It's come up repeatedly and so we can have to think about that in terms of claims data. How often would encephalitis and affective psychosis be confused or be differentiated in terms of how physicians would code what they do?

DR. LEWIS: That was actually one of the reasons why we did not put a lot of emphasis on these health claims databases. Because when we starting looking at the results, we recognized that they were looking

for very specific discharge diagnoses in that claims construction and that is quite different from the kinds of events that we might actually get captured in these case reports of adverse behavioral abnormalities.

So, yes, it seemed to be not capturing the kinds of events that we were really looking at. But in 2005, the committee specifically asked Roche to conduct these analyses and they did go to quite a bit of effort to both get the analyses done and then redid the analyses at our request to try and determine what might come up and there were multiple analyses done as you can see. There were just a very few events that even with small numbers came up as anywhere significant.

DR. ROTHSTEIN: The health claims data sets used by ICD-9 codes.

DR. HAVENS: But help me understand the difference just in reported by Roche and reported by Ingenix. I don't know. Ingenix is just another data collection. Tell me how

is Ingenix.

DR. LEWIS: It's a contract organization and Roche can describe this in much more detail during their presentation.

DR. HAVENS: Okay.

DR. ROTHSTEIN: Could I respond to that? I really think that you hit the head on the nail is that we presented this data because of the fact that we're trying to demonstrate it might be very good at picking up pneumonia but it's going to have problems in differentiating in the very area that we're trying to deal with differentiation.

DR. HAVENS: Yes. Absolutely. And the neuropsychiatric events that are the signal here are lost completely in any CDC reporting. They're lost almost completely except maybe for this in these big health claims databases and the reason that they get picked up by the FDA as a drug complication is that's the only place in this country that we have to report this kind of problem.

If we had an influenza reporting system that would account for this kind of detailed neuropsychiatric reporting, we might see that in adolescents with influenza in the first two days of their illness there was a very high rate of neuropsychiatric reporting or problems that last for a few hours to a day and is gone within 48 hours. The problem is that in this country we can only report that as an adverse drug effect.

So we can't really see it as an adverse disease effect or do the study in people with the disease comparing got drug versus didn't get drug. That's why the Japanese presentation was just so great today because potentially the sentinel physician survey of outpatient -- because this isn't hospitalized patients. It's not -- you know, the CDC think 85 percent of those kids had SIRS or sepsis. That's a completely different problem.

And so the neuropsychiatric diagnoses

-- the point has just been made that the ICD-9 codes do not map to the neuropsychiatric diagnoses that have been really developed by the FDA. Now the FDA has to give those diagnoses to the CDC and say, "Find these in people with influenza and then compare whether they got drug or no drug." And then you can see.

Good. Thank you for the answer. Sorry for the editorial comment.

CHAIRPERSON RAPPLEY: We're envious of the surveillance system in Japan. You can tell. Dr. Daum.

DR. DAUM: So I thought it would be really instructive to take advantage of Dr. Okabe's being here and ask him this question. Last time we talked about this as a committee and this time as well I'm really dazzled that people who live in Japan seem to have a very different concept of influenza than the rest of the world. They test for it. They're active about it and they prescribe way more

drug than everybody else in the world combined.

Can you give us a sense of what it is, what the attitude difference is, that makes people in Japan so on edge about this that they have this behavior that's so different than, say, ours or any other country's? The reason I ask is it might be insightful in terms of understanding what some of these reactions are.

DR. OKABE: So this is very difficult question to answer. Around 10 or 15 years ago, also that was a time when the immunization to the school-aged children was discontinued at that time and everybody, I mean, most of the people in Japan had no interest for the influenza. So we started a campaign what kind of the influenza and at that time, we said that American people or Western people could recognize influenza and the common cold. Influenza was a more fearful disease. That was as I said in the 10 or 15

years ago.

But nowadays, actually since was started the senior people's immunization and also influenza encephalopathy is a big issue for the young parents. So most of the people have an interest for the influenza situation. At that time, the antiviral drugs were introduced. Then that becomes a very popular and also at the same time, influenza diagnostic kit also had been introduced in the front level practitioners. So most of the pediatricians took the sample from the people and differentiate the diagnosis and if it is flu, okay. Give the antiviral and most of them are the Tamiflu. So attitude for the influenza may be now a very big difference. But for me, this is very difficult to say why a big difference occurred.

CHAIRPERSON RAPPLEY: Thank you. Robert Ward.

DR. WARD: I'd like to go back to the neuropsychiatric categories. We've made some

differentiations this morning between those with injurious behavior and those without and I'm not sure that those have any meaning at all. That is a child with delirium may respond one way that may be injurious or may respond another way and not be injurious.

What was the intent in separating those was it simply an effort to try to be comprehensive and capture all the neuropsychiatric events?

DR. ROTHSTEIN: We were trying to be comprehensive but distinguish between those cases that potentially could have resulted in an injury. The reason why we're very concerned about this is that there have been five deaths in Japan and there have been other situations where other people could have been injured. So we tried to separate those out into -- they are all serious adverse events, but this was a case categorization that we applied to try and make sense of the data and just lump the cases and focus on the ones we

were most concerned about just to see if we could identify patterns within the case categories.

DR. WARD: I can see how at a public health perspective it is important to be able to distinguish those that might cause or have caused harm. But I don't see that that manifestation of behavior separates those categories at all.

DR. LEWIS: No, they are probably part of the same spectrum. We did that purely to be able to try and identify cases that did or might have resulted in serious injury. But as you notice, both of those categories were at the top of the table and so these were looked at as part of a spectrum of events.

The descriptions are not that different except for the fact that some of them appeared to cause injury and some didn't and that may have been related to the age of the patient. A 14-year-old is much more capable of running out on a balcony, climbing

a four foot wall and leaping over than a three-year-old. So we recognize those things. It was merely a way to categorize events. It wasn't meant to say that these are different in some fundamental way from the other category.

CHAIRPERSON RAPPLEY: I do think it was helpful to have that description repeatedly of the urge to flee which seems to be a quality of this impulsive act. So I think in that regard it was helpful to separate it out to see that common thread there.

Dr. Kimberlin.

DR. KIMBERLIN: I have a question for Dr. Lewis. Your review of the developments in `05, `06 and so far in `07 in terms of the process, I apologize since this is my first meeting, I'm going to ask something most people around the room know the answer to already. In `06, you mentioned that the precaution section of the Tamiflu was changed

prior to the Pediatric Advisory Committee meeting. Was the Committee asked to endorse that change or comment in any way upon that change when the Committee did meet shortly thereafter?

DR. LEWIS: Yes. We did bring that to the Committee and I think if you looked at the background document I listed some of the additional recommendations that were made by the Committee. We had already been in the process after the completion of the `05-`06 flu season of working with Roche to amend the labeling because we had some other things in the label that were being revised at that time and so the timing was really somewhat coincidental but had been started not long after completion of our review of that flu season. But when we came to the Advisory Committee because it turned out to be kind of coincidentally close temporally, we did ask if there were other things that the Committee would have included and we considered those

and discussed them with the sponsor.

CHAIRPERSON RAPPLEY: Dr. Garofalo.

DR. GAROFALO: I just had another quick question of clarification because we heard this morning about the two sets. We're talking about like a severe encephalopathy, a coma, versus these more behavioral psychiatric adverse events and that there was a clear distinction within the Japanese data that the two are not related. So you don't start out with this behavioral event and then evolve. Would you say that's true of the data set here so that there's nothing different?

DR. ROTHSTEIN: Yes, that seems to be the case. There were a few events of what sounded more like a clinical encephalitis or encephalopathy and they were diagnosed that way and that there were many more of these descriptions of unusual behavior with or without other symptoms.

I would make one point. I was trained as a pediatric infectious disease

specialist and we certainly saw an awful lot of children with fever during my training and in practice after that and certainly children with high fever have delirium and have hallucinations and do some pretty bizarre things sometimes and so I guess that was one of the other reasons why we made a little bit of a distinction between the children who did something impulsive that was injurious and those who had what sounded a little more like the kinds of events that I had seen in children with febrile hallucinations and delirium. But I had never seen a child with fever just run out of a room and jump in front of a truck.

CHAIRPERSON RAPPLEY: Dr. Ward.

DR. WARD: Dr. Okabe or others in the room, this finding that oseltamivir can be a substrate for PGP and that there are SNPs, single nucleotide polymorphisms, that can decrease the activity of PGP and change the CNS penetration it seems to me like a

potential explanation of why specific people may respond to the drug as they have. Have you in Japan or anybody in this country done any genotyping of individuals who have had these kinds of reactions looking for something related, for example, to PGP?

DR. OKABE: Yes. Genetic analysis has been done among the influenza encephalopathy people but it has not yet concluded. So it will be done.

But regarding the abnormal behavior, I think the analysis is not yet done. So we don't have any answer for genetic differences between normal group for influenza -- encephalopathy, yes, maybe. However, abnormal behavior group it is not yet done.

But as I talked in the presentation, one of the differences between the Caucasian group and the Asian group particularly among Japanese people, the febrile seizure, the febrile convulsion, is higher in Japanese people. I think that is one of the hint --

however, it has also not yet clarified.

DR. LEWIS: And just one clarification. All of those potential explanations for greater adverse events have really been published within the last six months. So it's really relatively new information and I think there is a lot of work being done particularly in Japan to try and correlate what might have been identified either by modeling or computer searches for the SNPs and things like PGP activity and other metabolic and enzymatic processes.

CHAIRPERSON RAPPLEY: And there is I think a very concise review of that in our packet of information that you sent to us. I'm trying to see who offered that. You did. I thought that was well done.

DR. LEWIS: I tried to include those references also that we didn't have time to get them out to everybody.

CHAIRPERSON RAPPLEY: Yes. Other questions?

(No verbal response.)

CHAIRPERSON RAPPLEY: Okay. Thank you for those presentations. Very well done. I think we are ready to hear from our Roche representative.

I'm sorry. Yes.

DR. OKABE: May I have one question before his presentation?

CHAIRPERSON RAPPLEY: Certainly.

DR. OKABE: So actually in the United States, there are quite a few cases of influenza encephalopathy or not besides abnormal behavior? Because sometimes it is very difficult to diagnose and recognize just, yes, acute encephalopathy. So if the influenza diagnosis, whatever level of diagnosis, rapid test kit or etc., if you had done more laboratory diagnosis will it be increasing the number of influenza encephalopathy? That is my question.

CHAIRPERSON RAPPLEY: Yes. Dr. Kimberlin.

DR. KIMBERLIN: Did you say infant, like a young child?

DR. OKABE: Yes.

DR. KIMBERLIN: The NIAID Collaborative Antiviral Study Group, the group I work with, has completed a retrospective chart review of 180 or so medical records from across the country, the United States, for babies or infants under a year of age that were treated with an antiviral medication looking specifically for neurologic adverse events that might have been documented in this retrospective kind of a chart review process and we did not see any increase neurologic adverse events among babies treated with oseltamivir as compared to those treated with either rimantadine or amantadine.

In addition, there were no differences in the gliosarcoma scores and other more objective measures of their overall neurologic state. Now, of course, it is retrospective. It's 180 or so charts that

were reviewed. But at least it starts the process of looking specifically at that young age group to see whether there is any signs or symptoms that might suggest neurologic abnormalities or problems associated with any of the antivirals not including zanamivir and we did not see anything with that.

DR. LEWIS: One other comment to Dr. Okabe's question is certainly in the U.S. pediatricians in general when they have a child with an undiagnosed encephalitis or encephalopathy are very familiar with testing for herpes simplex virus and some of the -- whatever seasonal things like the arboviruses that might circulating. But I think particularly when it's not influenza season, general pediatricians are not in the habit of testing for influenza in a child who has an undiagnosed encephalitis or encephalopathy. So I think it's very possible that we might be missing a number of cases in that category just because they might be in a small

community hospital where the physician or pediatrician may not be testing specifically for influenza at the time of admission.

CHAIRPERSON RAPPLEY: Dr. Havens has a follow-up question.

DR. HAVENS: Just again to come back to the issue of nomenclature because you're using the term encephalitis or encephalopathy and if we focus on the concept that really seems to keep getting us here which is neuropsychiatric events, it would be my argument that people wouldn't even elevate these transient delirium or whether it's DEL or DIB or the miscellaneous one which is night terrors and insomnia, you wouldn't elevate that to the level of encephalitis or encephalopathy. So finding that signal is very difficult unless you're really looking for it.

DR. LEWIS: Yes. That's correct. But Dr. Okabe had asked about encephalitis in the U.S.

CHAIRPERSON RAPPLEY: Okay. Thank you and thank you for your patience and we'll look forward to your presentation.

DR. SOLSKY: Good afternoon. My name is Dr. Jonathan Solsky. I'm a Director of Drug Safety and Risk Management at Hoffmann-La Roche and today my colleague, Dr. Craig Rayner and I will be providing to the Committee an update of neuropsychiatric events that have been reported in association with Tamiflu. Today I'm joined with several subject matter experts from Roche who will be happy to answer any of the questions you may have after our presentation today.

I'd like to begin by giving a brief historical background. Dr. Lewis has done a wonderful job in terms of summarizing. I'm just going to briefly touch upon this. Tamiflu was approved in terms of pediatric exclusivity in 2004 and in the following year, November 2005, the Pediatric Advisory Committee met to discuss the safety profile of

Tamiflu. At that time, there were several reports of neuropsychiatric events predominantly coming from Japan and the Committee had recommended that the FDA return in one year and provide an overview of these neuropsychiatric events as well as any other unusual adverse events that may have occurred in the ensuing year and then in two years, both the FDA as well as Roche were to return and present to the Committee a comprehensive overview of these neuropsychiatric events that have occurred over the last two years as well as for Roche to provide an update on the health claims databases that we had access to as well as any additional studies that we may have conducted.

In addition, although not specifically requested by the Committee, Roche undertook several preclinical and clinical studies to further evaluate CNS penetration of Tamiflu as well as to explore pharmacological mechanisms that might account for these

neuropsychiatric events.

As you all know, Tamiflu is indicated for both the treatment and prophylaxis of patients one year and older. Currently, there is precautionary wording in the label that was based upon the risk assessment that was done in 2006 and as such the current labeling is present which reads as follows: "There have been post-marketing reports, mostly from Japan, of self injury and delirium with the use of Tamiflu in patients with influenza. The reports were primarily among pediatric patients and the relative contribution of the drug to these events is unknown. Patients with influenza should be closely monitored for signs of abnormal behavior throughout the treatment."

Today we're going to provide an update of the expended data sets that we have and based on Roche's medical opinion of evaluating these we feel that the current USPI precautionary label is an accurate assessment

of the current available data sets that we have thoroughly reviewed. Today we will be providing to the Committee an update in terms of seasonal Tamiflu usage by region and we will use this to place in context the spontaneous, post marketing safety reports that we have received. Since these reports are uncontrolled data, in order to explore the potential role of Tamiflu we pooled our clinical trials in pediatric patients who were being treated for influenza with Tamiflu and created an integrated safety database. In addition to this, given the relative rarity of these events, we also reviewed to large health claims databases to sort of compare these events in a somewhat controlled situation.

In addition, based on these results, we also attempted to explore the potential role of influenza. We utilized the U.K. General Practice Research database as a means of assessing neuropsychiatric events that would be reported in influenza patients not

taking Tamiflu versus a control group. In addition, we reviewed literature as well as reports from the Japanese health authority, MHLW's public website where there were reports of influenza patients that had neuropsychiatric events who had and who had not received Tamiflu.

In addition, my colleague, Dr. Rayner will come up to discuss with the Committee the clinical and preclinical studies that we did to explore possible pharmacological mechanisms to account for these neuropsychiatric events. This included systemic pharmacokinetics comparing Caucasians versus Japanese, CNS penetration of Tamiflu, looking at pharmadynamic parameters in terms of human neuraminidases and other molecular targets as well as exploring possible pharmacogenetic and drug-drug interactions and then I'll return to provide an overall summary of this body of information.

First, I would like to turn to the

seasonal Tamiflu usage by region. The following slide which I believe you have seen previously as well shows that in total since the approval in 1999 of Tamiflu 48 million prescriptions have been written. Seventy-five percent of those prescriptions as you've heard have been in Japan and when one looks at the pediatric population, one sees that approximately half of those total prescriptions have been written in the pediatric population. Furthermore, if one looks at the last two flu seasons, one sees that the Japanese usage is approximately threefold greater than that in the U.S.

Well, the question, of course, and the Committee has already raised this is why is the Tamiflu usage so much greater in Japan and as you've heard already, the clinical management of influenza appears different in Japan than it is the U.S. There is universal health coverage in Japan and although the vaccination rate in Japan is very similar to

that in the U.S. there is a much greater early consultation of influenza. Ninety-one percent of patients in Japan are seen within the 48 hours of the onset of their symptoms and almost as you've heard, all patients receive a point of care rapid diagnostic test which is reimbursed.

As an example using the 2004-2005 season, we noted that 60 percent of influenza patients had received antivirals and 83 percent of those received Tamiflu. And this may be due to guidelines that exist for the management of influenza with encephalitis and encephalopathy which do recommend Tamiflu.

I like to keep this usage data in mind as I turn now to the uncontrolled spontaneous post marketing safety reports and to first explain how we analyze this data, as you've heard from the FDA, we use a very broad case definition to define these neuropsychiatric events. We selected 51 MedDRA high level terms in both the

psychiatric and neurologic system organ class. In addition, we looked at the accident and injury system organ class also as a possible sequelae to delirium.

In terms of our issue work-up regarding this, we actually looked at all ages. But for today's presentation, we're going to focus solely on the pediatric population and we used the cutoff of less than or equal to 16 years of age which is a regulatory definition. In terms of looking at this information, we applied the 51 MedDRA high level terms to this pediatric subset database and identified 98 preferred MedDRA terms. All of these were the utilized in terms of cumulatively looking at all serious as well as non-serious neuropsychiatric events since approval in 1999.

We then looked at the subset of patients that had prophylaxis as an indication within our database. Furthermore, in order to characterize the events of most concern, the

serious neuropsychiatric events, we looked at those in terms of the last two flu seasons and what we did is we categorized them into 13 groups using a somewhat different scheme, an ICD-9 clinical scheme, and we then did further analysis using both the database as well single case medical review.

I just wanted to show you the list of the 13 categories that we utilized based on ICD-9 codes and I think later on you will sort of appreciate why we used ICD-9 as a schema if you will to look at other databases. But in terms of the 13 categories, we had abnormal behavior, cognition disturbances, delirium, depressed levels of consciousness, loss of consciousness, panic attacks, suicidal events, accidents and injuries, convulsions, delusions and perceptional disturbances, encephalitis, miscellaneous psych which included agitation, anxiety and restlessness and parasomnia which essentially consisted predominantly of nightmares. And these 98 preferred terms were

then collapsed into these 13 categories.

Looking at all the neuropsychiatric events, this includes serious and non-serious that had been reported since the approval in 1999 in the pediatric patient population, we noted that in total there were 55 patients with one or more neuropsychiatric events reported in the U.S., 1,745 in Japan and eight in the rest of the world. Taking into account the total number of prescriptions written that we had showed previously, one can calculate accrued overall reporting rate for each one of these regions and this comes out to 19 patients per one million prescriptions written in the U.S., 99 patients per one million in Japan and 35 in the rest of the world.

This is the cumulative data and we then went and looked at this from a standpoint of how this appears on a seasonal basis and the following slide shows you this information. What is striking here is the fact that in the last two flu seasons there's

been a marked increase in the number of neuropsychiatric events and the reporting rate of these events are higher in Japan than in the U.S.

Furthermore, when one looks at the subset of serious adverse events within this, one notes that the majority of events that have been reported from Japan were non-serious. Eighty-four percent of the total adverse events reported were non-serious from Japan and 58 percent in the U.S.

Well, we wanted to explore what could be the possible factors related to this increased reporting rate over the last two flu seasons. We looked and recognized that there had been no increase in the incidence of influenza versus previous seasons in Japan nor had there been any changes in drug manufacturing, formulation, dosage and administration.

However, we did note that there was an increase in physician and consumer

awareness. There had been reports of two fatal accidents in adolescents with abnormal behavior which resulted in MHLW's decision to restrict usage in 10 to 19 year olds in the Japanese PI in March of 2007. In addition, there were two "Dear Healthcare Professional" letters that had been drafted and sent out in Japan in both February and March of 2007. And the Japanese Health Authority had requested that physicians report neuropsychiatric events in influenza patients whether treated or not. In addition, there was increased Japanese media reports occurring over the last two flu seasons.

The following slide characterizes the serious neuropsychiatric events and the most frequently reported cases occurred in the following categories: abnormal behavior, convulsions, delusions and perceptional disturbances, delirium, depressed levels of consciousness and miscellaneous psych. Again, one sees that the reporting rate of these

cases is greater in Japan than in the U.S.

We decided to look at this data also in terms of when these events were reported in the last two flu seasons and the following slide looks at the 2005-2006 season and, in that particular season, we noted that the reporting rate in Japan was greater than in the U.S. and when one looked at the second season of 2006-2007, one sees a similar situation.

When one looks at the particular events that occurred in Japan that increased from the first to second season, one notes an increase in abnormal behavior, convulsions and loss of consciousness while in the U.S. this was in terms of delirium and delusions and perceptual disturbance.

We characterized these serious neuropsychiatric events that occurred over the last two seasons and noted that there was a similarity in the distribution of these events both in Japan and in the U.S. with the

majority of the reports occurring in the six to 12 year age group. Furthermore, we noted that there was a gender imbalance in terms of males where there was increased reporting. In the U.S., this translated into a 1.4 to 1 male to female increased reporting ratio while in Japan it was 1.8 to 1 male to female reporting ratio.

We looked at also in terms of the onset of these serious neuropsychiatric events and identified that 67 percent of these serious neuropsychiatric events occurred within two days after the diagnosis of influenza. Eighty percent of these events occurred within two days after the start of Tamiflu and in terms of those cases where fever had been reported, 44 percent of these cases were associated with fever. Clearly, these early events are occurring early after the start of the initiation of Tamiflu and they mirrored the systemic manifestations of influenza. Therefore, it becomes very

difficult to differentiate the causal role of drug from disease.

In terms of outcomes of these events, we noted that the majority of these events had a duration of less than one day. Eighty-seven percent had resolved or improved, 11 percent were not reported in our database and two were persisting. In total, 22 accidents or injuries were identified associated with these serious neuropsychiatric events and all of these reports were from Japan. There was an imbalance again, 15 males and seven females and the majority were occurring in the 11 to 16 year age group. Two of these events were not associated with a neuropsychiatric event.

In the last two flu seasons, there was a total of four fatality cases, all of which were reported from Japan. Three were fatal accidents, two males and one female in the 12 to 14 year age group and one case of encephalitis in a child with leukemia.

We also looked in total in terms of

the prophylaxis cases that we had in pediatrics and we identified six cases. All six of these cases were confounded. Three of the cases had documented fever with them and, in fact, in one of the cases with delirium, the patient was subsequently identified to have influenza and their dose of Tamiflu was increased to BID with an amelioration of the delirium. In addition, there was one case not suggested of a neuropsychiatric event. This was actually a case of loss of consciousness due to orthostatic hypotension. There was one case of encephalitis and there was one case of agitation that had started prior to Tamiflu. So thus, in all six cases, one could not attribute a cause directly related to Tamiflu.

In summary, in terms of similarities between the reports that had been coming from the U.S. and Japan, we noted that in all of these cases there was an early onset of these neuropsychiatric events, eighty percent of them occurring within the first two days of

start of Tamiflu and they were confounded by disease.

There was a gender imbalance in terms of males reporting more frequently than female and the age distribution was similar between Japan and U.S. with the majority occurring between the six to 12 year age group. Additionally, the majority of these events were self-limited and with no sequelae.

And in terms of differences, we noted the reporting rate which was greater in Japan. There were 0.4 patients with neuropsychiatric events per 10,000 prescriptions written in the U.S. versus elevenfold higher rate in Japan of 4.5 patients per 10,000 prescriptions written in Japan. In addition, serious accidents and fatalities have been reported from Japan.

I'd like now to turn to the attempts we made in terms of assessing the potential role of Tamiflu by looking at control data because the information that you have seen obviously is an uncontrolled data set and the

first thing that we attempted to do was again look at our clinical trials by pooling all the clinical trials where Tamiflu had utilized for treatment in pediatric patients.

The following represents our integrated safety database that we currently have for these clinical trials and 1,080 patients had received Tamiflu and 738 had received placebo. We applied the same methodology that we had done in terms of looking at our drug safety database and therefore used the 51 high level MedDRA terms which as I said is a very broad definition and applied this to the entire database and identified three cases on Tamiflu and two on placebo. These cases were of anxiety and irritability in both groups. There were no reports of delirium nor were there any deaths reported in this data set and therefore there was no difference in terms of the incidence of these neuropsychiatric events reported on Tamiflu versus placebo.

We also looked at our Japanese pediatric registration studies to see if we could identify something there. This was an open label study in 70 patients age one to 12 years of age with a median of four years. The adverse event profile was very similar to what we had seen in registration studies outside of Japan and, note this, no neuropsychiatric events were reported in this study.

While recognizing the fact that these events from our drug safety database are quite infrequent, we recognize that one needed to look at a much larger database in order to be able to even identify these cases and we looked at two large claims databases, UnitedHealthCare and MarketScan, and had done actually multiple analyses with these claims databases.

We initially started a study with Ingenix or i3 as they are now called and this was a drug safety study of neuropsychiatric events using their U.S. insurance claims

database, the UnitedHealthCare database. This was a study that included outpatients with a clinical diagnosis of influenza who were treated with Tamiflu or not treated with any antiviral therapy age one year or older. This particular study covered all flu seasons between 1999 and 2005.

Propensity scores were utilized to address for confounding in this study and to ensure comparable cohorts and three hierarchical categories of neuropsychiatric events were identified for study outcomes. The first highest category was any neuropsychiatric event. We then drilled down and looked at neuropsychiatric events but excluded chronic disorders, conditions with a stated etiology, congenital or hereditary disorders and spinal cord disorders. We then further drilled down and looked at neuropsychiatric outcomes specific to CNS stimulation and this was actually a composite of numerous types of claims, the list, as you

can see, up there includes psychotic disorders, the delusions, delirium, confusion, euphoria, hallucination and you can look at the rest of these. This is -- actually for the first way that we looked at, this was a composite of all these terms combined.

The analysis of this database in the pediatric population identified 20,501 patients receiving Tamiflu and a comparable cohort of 84,871 influenza patients not receiving any antiviral therapy. Based on the adjusted odds ratios in all three of the hierarchical outcomes, no increased risk was noted in patients receiving Tamiflu compared to those influenza patients not receiving any antiviral therapy.

A similar study was done with MedStat using their database, MarketScan, which is a U.S. employer based and Medicare claims database. This was a study that included outpatients with a clinical diagnosis of influenza treated with Tamiflu or not

receiving any antiviral therapy greater than zero years of age and quite similar to the other study except it covered flu seasons between 2000 and 2006.

In this study again, we did propensity score matching on patient characteristics and here again we used the composite as it relates to the psychiatric outcome which included events such as delirium, delusion, anxiety, psychosis, suicide and self-inflected injury.

The results of this analysis are shown on the following slide and in this particular study, 14,214 patients receiving Tamiflu and a comparable cohort of influenza patients not receiving antiviral therapy of 14,220 patients were identified. Based on the adjusted odds ratios for all pediatric patients as well as in the categories that are shown below of age groups, there was no increased risk of these neuropsychiatric events in patients receiving Tamiflu compared

to those not receiving any antiviral therapy.

Well, Roche actually gained access to both of these claims databases and our objective was to apply the same methodological approach that we had applied in our analysis of the drug safety database. In order to do that, we utilized identical selection criteria, age groupings, ICD-9 codes and categories for both of these databases. As I said, we used the same methodological approach in categorizing neuropsychiatric events into these 13 groups. We covered influenza seasons in both databases during the same time period of 2001 to 2006 and we included any neuropsychiatric event that occurred within 14 days of the index date. Here, too, we did propensity score matching to ensure comparable cohorts.

The following shows you the results of our analysis utilizing the UnitedHealthCare database. In the Roche analysis of the UnitedHealthCare database, we had identified

30,960 Tamiflu patients with influenza and a comparable cohort of 30,728 patients not receiving any antiviral therapy. As you can see from the slide above, for all neuropsychiatric events as well as for the other categories, neuropsychiatric categories, where events have been reported, no increased risk was noted in patients taking Tamiflu compared to those not taking antiviral therapy.

I would like to call the Committee's attention to the fact, however, that for many of these categories abnormal behavior, cognition disturbance, delirium as well as panic attacks and suicidal events, there were no events reported in these categories indicating the infrequency that these events occur. Furthermore, you will note that there are wide confidence intervals, for example, in delusions and perceptual disturbances, depressed levels of consciousness and, for example, parasomnia.

This reflects that small number of cases that we saw. In each of these particular categories, the number of events were less than five, again, indicating the infrequency in which these events are occurring.

We did the same analysis again, but this time looking at the MarketScan database and again applying the same methodology. In this case, we identified 26,287 patients who had received Tamiflu for the treatment of influenza and 26,153 patients not receiving any antiviral and similar to our analysis that we had seen with the UnitedHealthCare database again we saw no statistically significant increased risk of any of the neuropsychiatric events where events had been reported in the Tamiflu group compared to those not receiving therapy.

In summary, in terms of looking at the potential role of Tamiflu based on the clinical trials of influenza treatment where

we had integrated a safety database, we did not identify any difference in the incidence of these neuropsychiatric events in Tamiflu versus placebo. Furthermore, on the multiple analyses that have been done both by Ingenix and MedStat as well as Roche of the UnitedHealthCare and MarketScan databases, consistently the adjusted odds ratio results indicate no statistically significant increased risk in any neuropsychiatric event category in Tamiflu treated patients versus patients not receiving antiviral therapy.

Given these results, we then explored the potential role of influenza and what it may play in terms of these neuropsychiatric events. We did an epidemiologic study utilizing the U.K. General Practice Research medical database and we explored the neuropsychiatric events that were occurring in influenza patients versus the general population.

To further explain, this U.K.

database is a longitudinal medical database of over three million active patient medical records. This particular database was selected because in the U.K. Tamiflu is used in a very limited fashion. So we would not have any confounding in terms of use with Tamiflu here.

We identified patients diagnosed with influenza or influenza-like disease and we looked at the patients in the flu seasons between 2001 to 2006. The comparative group in this situation was the general GPRD population itself which comprises three million lives.

The same methodological approach was done as for the analysis we did with the drug safety database, again looking at the neuropsychiatric events categorized into 13 groups. We used a read coding which is how one looks at the General Practice Research database and maps directly to MedDRA. Patients were followed for 30 days after the

diagnosis of the neuropsychiatric events and we analyzed for all ages as well as the subset of patients, those less than 16 years of age.

The following shows you the results of this particular analysis. We identified 68,771 patients who had influenza in this particular database and, as I said, we used the comparator, the general population of three million and one notes that for all neuropsychiatric events as well as cognition disturbance, delusions and perceptual disturbance, depressed levels of consciousness, loss of consciousness and panic attack there is an increased risk in influenza patients compared to the general population.

Furthermore, we reviewed the literature to identify whether we could see similar cases to those that we had seen with Tamiflu in patients not treated and we found from Japan actually two articles, review articles, that identified several cases of patients had similar neuropsychiatric events

to that that we had seen on Tamiflu in patients who had influenza and the onset of these events occurred within the first 24 hours of illness.

Similarly, in review articles from Taiwan, we found three which again conveyed information regarding similar types of neuropsychiatric events in influenza patients who had not been treated. These included events of visual hallucinations, seizures, personality changes and abnormal behavior and again these events occurred soon after the onset of febrile illness.

Furthermore, we explored MHLW, the Japanese Health Authority's website, and there is information of cases of patients with influenza who have received treatment as well as not having received treatment and we focused here actually on the cases of no antiviral treatment or patients receiving amantadine or zanamivir.

We identified there were 25 patients

with neuropsychiatric events who had not received any antiviral therapy, five on amantadine and 12 on zanamivir. Interestingly, the male gender imbalance that we had noted in our database we noted here as well, a two to one reporting ratio and predominantly these events were again occurring in the pediatric population.

In terms of the distribution and scope of these neuropsychiatric events, they again fell into the similar types of categories that we had identified and, in fact, there were even unfortunately serious sequelae including death in the case of a patient not receiving antiviral therapy and in the case of amantadine.

Furthermore, there are narratives on this public website and we pulled those examples, three of these, which are strikingly similar to the ones that we have seen on Tamiflu. These include narratives from a patient not receiving any antiviral therapy as

well as a patient receiving zanamivir and amantadine.

The one constant one notes in all of these cases similar to Tamiflu is influenza.

In summary, there is emerging information that suggests a potential role of influenza. Based on our analysis of the GPRD database there is a suggestion of a 1.75 to 2.5 fold statistically significant increase in risk for neuropsychiatric events in these influenza patients compared to the general population. And in terms of reviewing information from both the literature as well as the Ministry of Health's public website, similar neuropsychiatric events in influenza patients not receiving Tamiflu appear similar to those reported with Tamiflu. They are mainly in children and adolescent patients. There's a reporting imbalance in males. These events occur early in the course of influenza illness and temporal association with fever and delirium and behavioral abnormalities

which infrequently lead to injury are reported as well.

I'd like now to turn over the podium to my colleague, Dr. Rayner, who will discuss the further work that we have done both preclinically and clinically to explore possible pharmacological mechanisms to account for these neuropsychiatric events.

DR. RAYNER: Thank you, Dr. Solsky. So the FDA has requested that we provide an update on Roche's evaluation of the possible pharmacological mechanisms for the neuropsychiatric adverse events.

What I would like to do is to give a little bit of insight into our evaluation of not only new studies which we have been performing but, in addition, reanalyses of our original development program. And what I would like to do is to focus on four main areas: systemic pharmacokinetics where we were evaluating potential differences or the similarities between Japanese and Caucasians;

the extent and also mechanism relating to the penetration of Tamiflu within the central nervous system; pharmacodynamics particularly looking at if Tamiflu can reach the central nervous system are concentrations high enough to actually elicit an effect on neuraminidase which is the target of the compound or other molecular targets; and also as we've heard some discussion today on potential pharmacogenetic or even drug-drug interaction mechanisms that could be underpinning these events in Japan.

What I'd like to do is now to move to the systemic pharmacokinetics, but for the Committee just to recap on a couple of fundamental issues with Tamiflu pharmacology. The first is that Tamiflu contains oseltamivir which is a prodrug. It's an ester prodrug and it's absorbed very rapidly and then it goes to the liver and it is rapidly and extensively converted into its active form, oseltamivir carboxylate. It is the

active metabolite which causes neuraminidase inhibition. It prevents viral replication, limits the severity of disease and also the duration of illness. So it's these two moieties that we have to consider when we're thinking about pharmacokinetics.

I guess as a conclusion, to start with a conclusion, there are no clinically relevant systemic pharmacokinetic differences which we have been able to glean between Japanese and Caucasian adults and children and this comes from two main areas of evidence. The first is that of a head-to-head comparison of Japanese and Caucasian adults that was conducted during the development program and in this study, two separate doses of Tamiflu were administered, 75 milligrams and 150 milligrams, to Japanese and Caucasian health adult volunteers.

I'll direct the Committee's attention to these panels here. On the y axis we have plasma concentrations and on the x axis we

have time. The first panel is looking at the prodrug, the second panel at the active metabolite, and as you can see with the two separate doses here, the average profiles are effectively superimposeable. So this underpins that there do not appear to be dramatic differences. There is quite a lot of similarity in the pharmacokinetic profiles in adults.

As far as Caucasian and Japanese children are concerned, there is limited data with this, most SPARSE sampling from our development program and what we do know is that the concentrations from Caucasian and also Japanese children in our development program in terms of prodrug and also metabolite overlap. So again, there is no signal for the differences in pharmacokinetics even within Japanese and Caucasian children.

And as a point of clarification, there was some discussion around the table a little earlier which talked about differences

or similarities in dosing regimes between Japan and also the U.S. I'd just like to clarify that, in fact, in Japan the dosing regime is two milligram per kilogram whereas in the U.S. the approved dosing regime is actually a weight-based unit dosing approach which is subtly different.

So we now move onto the CNS penetration. We've recently completed a clinical study in which we examine the CNS penetration of Tamiflu. We looked in healthly volunteers following a single dose of 150 milligrams of Tamiflu for the concentration of the prodrug and the metabolite within CSF and also at the same within plasma.

What we can see here are the results. We have the concentration on the y-axis. We have the time in hours on the x-axis. The plasma concentration is denoted in blue and the red is the CSF concentrations. We can see here limited extent of penetration.

Now while this study was not powered

to actually look for comparisons between Japanese and Caucasians, what is important to see is that there is limited penetration and no overt differences. We're looking at approximately two to three percent CFS to plasma ratios. That's the prodrug.

And similar findings can be seen for the metabolite. So again, on the y-axis is concentration. On the x is time in hours. And in terms of CSF to plasma ratios between the two populations, we're looking at overall around three to four percent.

And we also have recent nonclinical studies which suggest that CSF may be an appropriate marker for brain concentrations as well.

Now while that study that was just presented is in healthy volunteers, there is unfortunately very limited information in the literature in influenza infected patients. There are two cases.

The first is a 10 year old male

Caucasian with influenza B encephalitis. In this case, plasma and CSF samples three hours after the last dose of oseltamivir 75 milligram twice a day were taken and the prodrug and the metabolite was quantified in plasma and the concentrations were consistent with expectations. However, there was nothing that was detected within the CSF.

Another case, a recent case, was that of a 13 year old male, a Japanese male, who had fallen to his death from a building. The subject fell approximately six hours after a single dose of Tamiflu. Autopsy samples for the metabolite showed the blood concentration actually consistent again with expectations for that time. The metabolite concentrations were not higher than the lower limit of quantification of the assay in several brain regions and this was an autopsy case.

The prodrug was not detected in any tissue tested. There was a caveat though for this and that is the forensic laboratory used

an analytical methodology which is not as sensitive as we would in our clinical studies at Roche. But what we can say is that the lower limits of quantification for the assay are still more than 85 times less than concentrations which we have evaluated where there is no relevant activity on more than 150 targets and this will become evident in the following slides.

So we move to the pharmacodynamics. The prodrug and the metabolite through our investigations do not have any relevant effects on human and other mammalian pharmacodynamic targets.

The first line of evidence for this is that there is no relevant activity at more than 150 different mostly human targets including those relevant for emotional behavior such as dopamine and MNDA receptors and this is at concentrations up to 30 micromole. We looked not only at the off-target effects, but neuraminidase which is the

target for activity and inhibition of mammalian neuraminidase requires more than 1,000 times the therapeutic plasma concentrations and this is denoted in the figure below.

Here we have an experiment based on monkey brain neuraminidase. On the y-axis we have the activity and on the x-axis we have concentration. These represent a number of experiments looking at the prodrug and also at the metabolite and inhibition does not occur until you're reaching concentrations well in excess of 1,000 times the plasma -- and it's another order of magnitude to the CSF concentration and as you can see in terms of selectivity the KI for viral neuraminidase is in the nanomolar range demonstrating the highly selective nature of the compound.

We've looked at the systemic pharmacokinetics, penetration, pharmacodynamics. Now given the rarity of these events, we wanted to explore some of the

things which have been described today in terms of pharmacogenetics or whether or not there could be a drug-drug interaction which is underpinning these events that have been observed in Japan.

We performed a number of nonclinical studies which identified molecular targets where if genetic polymorphisms were to arise we could investigate these molecular targets and try and understand if they are likely to have any effect and the conclusion that we came to was that the available data including some of the discussions today suggest that pharmacogenetic basis for these events are unlikely.

The first point, carboxylesterase is the enzyme which is responsible for the liver conversion of the prodrug to the metabolite. We wanted to look at some hypothetical scenarios. There is no evidence to suggest that there is a clinically relevant polymorphism through this pathway.

Nevertheless, what we wanted to do is to examine the what-if scenario.

We built a population pharmacokinetic model based on available clinical data. We inhibited any metabolism opportunity and then we simulated what those prodrug concentrations might look like. And then we compared it to the available concentrations which have been seen in other clinical pharmacology evaluations and what we actually identified was that even if carboxylesterase was not functioning through some hypothetical polymorphism we would not expect the concentrations to be problematic as we have concentrations in the clinical pharmacology studies which exceed these and no known neuropsychiatric adverse events have been observed.

As we've heard today, P-glycoprotein as we have also identified exports the prodrug from the brain as well as passive transport, of course. We went through another scenario,

the highly unlikely scenario, that a polymorphic variant might exist which through our evaluation is not supported and again we did simulations and in the absence of PGP export, the predicted brain levels of the prodrug are still expected to be well within established safety margins.

The other area where polymorphic variance might arise is that for the tubular secretion of the compound. The metabolite is a weak substrate for renal tubular secretion through OAT1. We had actually performed a study with probenecid which ablates this pathway. We noted a two and a half fold increase in concentrations in that study. No neuropsychiatric adverse events were noted.

Again, available data today suggests pharmacogenetic basis for these events is unlikely.

We also performed a drug-drug interaction assessment. Oseltamivir itself has low DDI potential. There's no role for

CTP450 or Phase II pathways. Clinical studies, we have already performed show no drug-drug interactions with influenza concomitant medications such as acetaminophen, aspirin, amoxicillin.

We then performed a directed drug-drug interaction assessment of the serious neuropsychiatric adverse event cases in the Roche safety database. No concomitant medications were reported in 54 percent of occasions for all and 30 percent for serious. We were unable to uncover any signal for a drug-drug interaction in the serious cases following a systematic literature review of some 161 concomitant medications examining for the potential for carboxylesterase, PGP and OAT1 interference. So overall, we were unable to identify any unifying hypothesis for a drug interaction.

In conclusion, the systemic pharmakinetics between Japanese and Caucasians appeared very similar. There is limited CNS

exposure to Tamiflu. At concentrations well above therapeutic doses, there are no relevant effects of either the prodrug or the metabolite on human targets. And we were unable to identify any plausible pharmacogenetic mechanisms related to the events or any drug-drug interactions.

But nevertheless we remain vigilant and we are continuing to do further studies. We have a number of nonclinical activities still underway looking at disposition, also potential activity. We also have some directed clinical assessments and we've heard from two of our speakers today already of a polysomnography study which we are conducting in collaboration with MHLW colleagues that are conducting and this underway and we also have a collaborative study being run by the National Institutes of Health, the collaborative antiviral study group in infants under the age of 24 months which has directed assessments.

At this time, I'd like to now invite Dr. Solsky to please come up and provide concluding remarks.

DR. SOLSKY: In summary, in terms of the body of information that you have seen today, in assessing the potential role of Tamiflu based on pooling trial data as well as review of claims databases, we have not identified any increased risk of the neuropsychiatric events in influenza patients taking Tamiflu versus those not taking drug. We have not identified any pharmacological mechanism to account for these neuropsychiatric events. We've noted, however, that there is some emerging evidence that further supports the role of influenza from sources such as the U.K. Medical Database GPRD as well as literature and reports on the Ministry of Health's website.

Based on our update of the post marketing reports, the majority of these reports are coming from Japan and

predominantly in children and the majority of these delirium-like events occur early in the course of influenza and early after starting Tamiflu, therefore making it very difficult to differentiate drug from disease and thus we can definitively exclude a contribution by drug.

Nonetheless, given the totality of information, a causal relationship to drug has not been established. In light of this, it is Roche's medical opinion that the current Tamiflu neuropsych U.S. PI labeling to be an accurate assessment of all available, updated and expanded data.

However, given the uncertainty, what role, if any, Tamiflu may play in these events, we are committed to doing additional future activities and that is to continue post marketing pharmacovigilance as well as Dr. Rayner has described to you continue the on-going, nonclinical and clinical studies to assess CNS involvement. Furthermore, it is

our intention to initiate an observational cohort study with Kaiser to estimate the background rates of neuropsychiatric events in patients with clinically diagnosed influenza as well as laboratory confirmed influenza and to assess Tamiflu treatment versus untreated patients.

Thank you for your attention.

CHAIRPERSON RAPPLEY: Thank you very much. Open for clarifying questions.

DR. WARD: Dr. Rayner, could you tell us the sample sizes fo those studies that you presented on slide 59 about the carboxylesterase inhibition, P-glycoprotein and probenecid?

DR. RAYNER: Yes. If I might just clarify, that's the pharmacogenetics slide. Correct?

DR. WARD: Correct. Yes.

DR. RAYNER: So I'll start with the the bottom, the probenecid.

DR. WARD: Yes.

DR. RAYNER: It is -- and I can't remember the exact number, but it's approximately around 14.

DR. WARD: Okay.

DR. RAYNER: In terms of the other two, in terms of PGP and carboxylesterase, they are simulations. This is based on simulated data. What actually supports the simulated data for the carboxylesterase example is actually five clinical studies with approximately 140 patients. In addition, approximately 140 patients for which a population of pharmacokinetic model was then developed. So there's a quite a substantial amount of clinical data underpinning the models which were used to make those claims.

DR. WARD: Would you describe the PGP model a little bit more, how that was conducted?

DR. RAYNER: Sure. The PGP model itself was performed using using a physiological base model, a PBPK model with

gastroplus and that model uses some very high level assumptions just based on physiochemical properties and unbound concentration data and what it actually does is it provides a simulation of what might happen in the central nervous system in the absence of any active transport process. So that was the most conservative approach that we had used.

Another approach which we actually used was based on the Morimoto data. In the Morimoto data, they actually talk about a sixfold change in knockout mice and on that basis, we also multiplied out expected concentrations in the central nervous system in humans by sixfold. So we had done this in a number of ways.

DR. WARD: And after that multiplication, the levels were substantially less or around three or 30 micromoles?

DR. RAYNER: In terms of PGP?

DR. WARD: Yes.

DR. RAYNER: In terms of PGP,

substantially less.

DR. WARD: Okay. Thanks.

CHAIRPERSON RAPPLEY: Dr. Kimberlin.

DR. KIMBERLIN: I have two questions, one for Dr. Solsky to begin with. On slides 35 and 36, the UHC database and the MarketScan data are represented and the sample sizes for the UHC database were around 30,900 for the Tamiflu group and 30,700 for the no antiviral therapy. But on a different slide, slide number 30, the UHC database had sample sizes of 20,500 and 84,900 and then similar kinds of discrepancies and sample sizes for the slides in the MarketScan. Can you clarify why there are differences in those samples sizes?

DR. SOLSKY: Again, this is because of the differences in terms of the methodology that was employed. That's because the first analysis was done actually by i3 and they applied -- again, I can't speak directly to it, but I'll have the expert in our group in terms of epidemiology, Dr. Susan Sachs, to

come up to explain to you. But just to explain that the i3 analysis was an independent analysis. It was not conducted by Roche and then subsequently what you're looking on the Roche analysis, if you will, was a secondary analysis to try and link what we had done with our drug safety database to make it more germane really in terms of the events of concern and try and capture that. Because actually the discussion the Committee was having earlier that when we looked at what i3 had done, many of these events were not really the events of concern and interest. So that was the reason for it. But I'd like to bring Dr. Susan Sachs from Epidemiology to also address the issue.

DR. SACHS: The reason for the difference in the numbers, when i3 or Ingenix did the first analysis they used the propensity scores to stratify patients by quintiles. So basically they calculated a propensity score for each patient and then put

them in strata. So they ended up with however many Tamiflu patients and then however many non-antiviral.

The way when we did the analysis, we founded the MarketScan method of matching a case and control by propensity score. So we were matching people on propensity scores. You can see we have similar sample sizes. So it's just two different methods.

DR. KIMBERLIN: And the second question is for Dr. Rayner. On slide 51, there are data that are represented graphically on the top, Japanese and Caucasian adult volunteers. This is the systemic pharmacokinetic slide and those are easy to grasp in terms of the way they're represented and then the bottom part of this slide is really simply numbers that are stated. Is there a way to get more information either graphically about that or as well that was the slide where you paused and said that in Japan they used 2 milligrams per kilogram per dose

of oseltamivir. Is that the dose that represents the Japanese data versus the way that it's dosed in the United States? Are we comparing apples to apples here?

DR. RAYNER: Yes. Let me address both of those questions. If we could please have slide up. So this was also supplied in the briefing package and I apologize that it probably wasn't as easy to see as one would like.

This actually is for the prodrug and this looks at Japanese and Caucasian children. This is actually normalized doses to two milligram per kilogram. So we are comparing apples with apples here. This is Caucasian and Japanese children.

The point to make here is that a lot of this comes from -- there were some intensive studies. There are some SPARSE studies. The reason why there are different times is just simply the dosing interval from which they were actually obtained. So what you

should be focusing on here is these green dots versus all of the other dots and that was what I tried to capture in the bullet points. The conclusion here is that the concentrations really are comparable. There are no significant outliers for the prodrug.

If we actually move to the carboxylate one as well, you can see another single -- now the second point that, slide down please, I'd actually like to address is that of the differences of dosing, yes, in Japan versus the rest of the world. That data which I showed you there was based on the clinical trials in pharmacology database and we're comparing apples with apples.

What is actually happening in real life in Japan versus the rest of the world? If I might have the slide up please, this is the exposures on the y-axis. What we have actually here is age on the x-axis. This dotted line is the average concentration for adults who are receiving 75 milligrams twice a

day.

Up here is adults who had 150 milligrams twice a day. This is also from the Phase III studies. There were approximately 450 adults in the Phase III studies who received this dose. And what we have here are the two average profiles for what you would expect to see with children of the following ages based on ideal body weights.

This is a flat two milligram per kilogram dosage and after 13 years of age, the dosing is actually identical. So the profiles are parallel after that. What you can actually see that overall the Japanese children are actually exposed to approximately 10 percent less drug with their dosing regime as to what happens in the rest of the world. The bumps are actually where the unit dose kicks in.

Overall, what you're actually seeing is there are some subtle differences. The concentrations do sort of hover around what we

have seen with the adult dosing and there are some subtle differences between the two populations. But overall, the Japanese are exposed to approximately ten percent less. Slide down please.

CHAIRPERSON RAPPLEY: Dr. Newman.

DR. NEWMAN: I guess this is just another quick question for Dr. Sachs. If the healthcare databases were analyzed by individual matching, then I'm just puzzled why aren't the sample sizes of the exposed and unexposed exactly the same.

DR. SACHS: I don't know. Our programmer is not here to answer that question. I don't know why they're exactly not alike. There probably might have been an exclusion for missing values or something like that. But they're almost identical. I mean they're very close.

DR. NEWMAN: Yes. It just doesn't quite make sense because if you excluded the control, you would -- I mean if you had

excluded -- you would have exclude the matching case. Right?

DR. SACHS: Yes. I can't tell you why they're not exactly the same, but I know for a fact that she attempted to match one for one. So I can't tell you exactly that. Ask me another question.

(Laughter.)

CHAIRPERSON RAPPLEY: Dr. Daum.

DR. DAUM: This is a generic question for, I guess, both Hoffmann-La Roche presenters. It goes under the future plans category. We've sort of -- I think the Committee has sort of latched onto the idea that more data regarding prophylaxis of oseltamivir would be useful among people that don't have influenza. Perhaps that would be an opportunity to at least partially sort out this phenomenon.

Did you consider when you made this slide of future activities or discuss or would you be willing to discuss whether a large

scale study of prophylaxis might be helpful in several ways among them informative about neurologic complications?

DR. SOLSKY: I think we've looked both at it in terms of treatment as well as prophylaxis in terms of doing actually a clinical studies and there are actually several challenges in doing either one of these. First as you can appreciate today, there is really a difficulty in terms of the case definition and what exactly is the event we're trying to capture. So what is the endpoint truly?

Secondly, is the subjective nature in which these events have been occurring and in terms of how they're communicated. That's also somewhat difficult because you would want to have more objective kind of criteria.

But I think one of the other issues that we've done is we've tried to actually even look at the feasibility of trying to conduct such a study and I'll talk first about

treatment and then I'll talk about --

In terms of treatment, I would like to bring slide up, we used our claims database to just to look at essentially what would be the background rate of delirium-like neuropsychiatric events. Based on the claims database and pooling both the UnitedHealthCare as well as the MedStat database, we identified a background rate of about six per 10,000 patients and this remember is a very broad definition. It's not the real specific definition of the issue of concern which is the impulsive behavior with delirium which then would make the background rate much lower even than what it currently is listed here.

Nonetheless, using a six per 10,000 rate if one were to even show a 50 percent increase in the Tamiflu arm, one would need 130,000 patients per arm or a quarter of one million patients.

We've looked at prophy as well and I can say that both in terms of reviewing the

events that we have in our database we agree with the FDA that we had 19 cases of prophy and we looked at those cases and didn't find any signals. We also looked at prophy in terms of trying to do a study with our claims database which would naturally be the next way to handle this.

There is a great deal of difficulty in actually identifying prophylaxis cases in claims databases. The issue that comes up with this is the fact that while patients can end up getting a prescription and there isn't a diagnosis there, it becomes questionable is it truly that they're getting prophylaxis or are they getting treatment and it hasn't been captured. If you think about it, someone can call their physician and say, "I want a prescription." You get a claims, but you don't get a diagnosis. So that's one issue.

Even if there is a diagnosis that is in the claims database, the issue then becomes in terms of when exactly do they take the

drug. Because obviously to match up the neuropsychiatric event after the time of the administration drug, it's very dependent upon when the patient first starts taking drug. If they're getting it for prophylaxis, we can't assure exactly when they start and when they complete. All we know is that we have a claim that they wrote a prescription.

So there is a lot of difficulty actually and challenges in trying to use even the claims databases. We're still exploring possibilities actually to be honest with you in regards to this because we would agree. The prophy is sort of an area that we think we could possibly tease out more clearly this issue. But at the moment, we're sort of stymied with that and that's sort of where we remain.

Therefore, just to talk about our future plans, finally --

CHAIRPERSON RAPPLEY: Could we delay talk about future plans so that we could have

the two remaining questions that we have and then our next presentation?

DR. SOLSKY: Okay.

CHAIRPERSON RAPPLEY: If that seems acceptable to the Committee. Thank you. Dr. Cnaan.

DR. CNAAN: Yes. I have two questions. One for Dr. Sachs regarding the propensity scores. What were the components that went into the propensity?

DR. SACHS: Can I have the slide up please. For people who don't know, I don't know if everybody here is familiar with propensity score matching, but it's basically a method to try -- because this isn't a clinical trial where you can randomly assign people to a drug or a no drug, it's a method of trying to make the people on treatment somewhat similar on many aspects to the people who are not on treatment and so you basically do like a regression of prediction of taking treatment and then use those variables for

both groups.

Here you can see from the second bullet the propensity score matching took into account age, gender, region, presence of fever or pneumonia and medical history and in your briefing documents or at least in the reports that we submitted to the FDA, we showed that the patients looked very much the same according to baseline characteristics once the propensity score matching had been accomplished. Does that answer your question?

DR. CNAAN: Yes. Thank you. That's very helpful. Just a comment, I guess to Dr. Newman. What may have happened is that there were these few patients who did not match up, so they didn't find a control, and while they matched to get the sample, they didn't do a matched analysis. It's not clear for me that it was a matched analysis and that would explain the unequal numbers. That's just a comment.

I have a question for Dr. Solsky

regarding 35 and 36 again. There were a number of categories where there is no confidence interval because it's not applicable and, of course, there are the ones that are the most interesting like abnormal behavior and a few others.

DR. SOLSKY: Slide up please. Yes.

DR. CNAAN: Why is that?

DR. SOLSKY: I think it just points out the infrequency of these events. If you think about it, it's really a database of 60,000 patients and we didn't identify one of these events, for example, delirium, abnormal behavior, these cognition disorders and we actually used several different ICD-9 codes as well in order to capture this in terms of the mapping into this categorization process itself.

But we actually had no events in either the Tamiflu group or the no treatment group for those particular categories to even be able to calculate an odds ratio.

DR. CNAAN: So I guess my question is taking delirium how would you explain that given the quick infrequency that we saw either in the Japanese or U.S. data sets.

DR. SOLSKY: I think what we're seeing actually in terms of delirium in the context, remember, of the total number of prescriptions written is that this is actually a very infrequent event. If you look at, for example, the reporting rate that we have in the U.S. and this is based on a drug safety database, it's 0.45 per 10,000 patients. So again, very small number here.

CHAIRPERSON RAPPLEY: Two more questions. Dr. Gorman.

DR. GORMAN: Being a pediatrician in practice for many years, it's hard to capture neuropsychiatric events because there are no codes for them. So the concept of a pediatrician writing down at the bottom of a chart "abnormal behavior" and then going to the DSMV and finding the code for that, it's

just not going to happen. So using claims databases for pediatric diseases to find neuropsychiatric events I think is -- I'm amazed you found as many as you did. So I would compliment you on finding some. Some pediatricians must be much more obsessive, compulsive than myself.

Having said that, I have two questions that deal with your databases. In the general practice research database that you used in England, did you -- when you compared the two groups, did you compare them over the same time period?

DR. SOLSKY: Actually, I believe that comparative group was in the 2004. I'll bring up again our expert in that.

DR. SACHS: The way the comparative group was composed was that all patients in the general practice research database who were alive and in the database on January 1, 2004 which was three million something made up the comparator and the treatment groups were

by season for those patients with influenza during those influenza seasons actually starting, I think, in 2001 through 2006.

DR. GORMAN: Do you think it's possible that a general practitioner faced with a patient with pneumonia, I'm sorry, with influenza or influenza-like illness in his office might be less likely to comment on their neuropsychiatric behaviors than someone who comes in with a chief complaint of depression?

DR. SOLSKY: I think it depends on the seriousness of the nature of the neuropsychiatric event. In a situation that we're talking about today, I think there is, as you've seen, sort of a spectrum of a neuropsychiatric events. The ones that are the most disconcerting I think those a pediatrician would report.

However, I do acknowledge the fact that those that are less serious we would not hear about nor see.

DR. GORMAN: The concern I have is that most people do charting for reimbursement and influenza is a reimbursable charge and most neuropsychiatric behavior disorders are not.

CHAIRPERSON RAPPLEY: Dr. Ward.

DR. SOLSKY: But that's not the case in the U.K.

DR. GORMAN: I'm not aware of the case in the U.K. I'm sorry.

DR. WARD: This is for Dr. Solsky. At last year's PAC, the label was changed just prior to that meeting and I have concerns about the labeling for the child under a year of age based on the animal data alone since the mortality is as high as it is in that particular age group. I know the pharmacokinetic studies will be undertaken very soon, hopefully this season, in that population. Will you consider changing that label if there is not a safety signal?

DR. SOLSKY: We have already some

information in terms of patients under the age of one currently already and it's more in terms of both the ongoing trials that are exploring this population as well as safety information and from that, so far we haven't found any untoward reactions in that age group in comparison to the safety profile in general in patients over the age of one.

I'd like to also bring up my regulatory colleague who will address the other issue.

MS. CAREY: Ellen Carey, Regulatory Affairs, and I just wanted to mention that NIH is currently conducting a study in children under one and based on the results of that data, we would have a discussion with FDA if it was appropriate based on the results of that study.

CHAIRPERSON RAPPLEY: Am I correct that in looking at your UnitedHealthCare data you, Roche, analyzed that data, Ingenix analyzed that data, same data set, two

different methods? Your results indicate no increased risk for these unusual events. The Ingenix indicated increased risk for affective psychosis. Am I correct?

DR. SOLSKY: What one needs to appreciate is as I presented, it actually was a composite of a multiple of terms initially and so what ended up -- what one first needs to appreciate is that first hierarchical whether it was a composite and then subsequently, there were all of the particular terms like effective disorder and in terms of the multiple looks that were done for looking at those individual terms there was no correction that was done in terms of the confidence intervals.

CHAIRPERSON RAPPLEY: I'm not really asking for an assessment about which method was better. So there were two different methods used.

DR. SOLSKY: Yes.

CHAIRPERSON RAPPLEY: Your method

indicated that there was not increased risk. The Ingenix method indicated increased risk for affective disorder as reported by you, Dr. Solsky. I just wanted to clarify that.

DR. SOLSKY: But again, in order to understand that, the rolling up of that into the composite term of CNS stimulation did not show that. So it was just one event of the multiple of different terms that were looked at.

And can I bring this slide up just to further clarify this. If one looks at this slide, one notes that the only odds ratio that was statistically significant was in regards to the effect of psychosis. For all of the other events, one notes that they were not. And again, there was no correction that was done for the multiple different events that were looked in terms of the individual terms.

CHAIRPERSON RAPPLEY: Thank you. I think we should move onto the Glaxo SmithKline presentation. Is that agreeable to the group?

(No verbal response.)

MS. NUNCASHIN: Hello. My name is Judy Nuncashin (phonetic) and on behalf of Glaxo SmithKline, we thank the Advisory Committee for the opportunity to present the safety data for zanamivir for inhalation.

Today we will highlight the safety information as it relates to the pediatric population in the areas of neurology, psychiatry and injury.

Since the beginning of the clinical development of zanamivir in 1993 through the registration and marketing of Relenza, GSK has performed routine pharmacovigilance and monitoring for any emerging safety signal. This standard surveillance has not revealed any concern for an association with neuropsychiatric adverse events.

During the 2004-2005 influenza season, we became aware of reports of neuropsychiatric adverse events associated with oseltamivir from Japan. Since zanamivir

like oseltamivir is an anti-influenza neuraminidase inhibitor, these reports prompted GSK to undergo a more thorough safety review. This was completed in November of 2005 and included clinical trials data from both centrally-sponsored registration studies and studies conducted within Japan as well as post marketing reports. This review concluded that there was no association between zanamivir and neuropsychiatric adverse events and surveillance continued as usual.

In the spring of 2007, there was a spike of reports of neuropsychiatric adverse events in patients receiving zanamivir from Japan. After GSK submitted the first group of these reports to the FDA, the Division of Antiviral Products requested a further analysis of the zanamivir safety data including data from the most recent influenza season. This review was completed last month and again concluded no association between zanamivir and neuropsychiatric events. We

continue to employ our standard pharmacovigilance practices with special attention to any neuropsychiatric events.

We will present the details of our comprehensive review and analysis of all the available safety information here. From these activities we conclude that zanamivir does not demonstrate evidence for a causal role in neuropsychiatric events during the treatment of prophylaxis of influenza infection. Moreover, no revision or update to the U.S. prescribing information is warranted.

For this comprehensive safety analysis, we considered many data sources including the preclinical animal studies, the pharmacokinetic characteristics of zanamivir, the clinical trials safety database, safety surveillance within Japanese drug utilization investigations as well as published literature on zanamivir and the epidemiology of influenza-associated neuropsychiatric manifestations. Finally, we undertook an

exhaustive review of the GSK safety database that includes spontaneous reports, post marketing surveillance and unblinded serious adverse events from clinical trials.

Within the preclinical toxicology program, multiple animal studies were performed wherein rats, mice, rabbits and dogs received zanamivir by inhalation, oral or intravenous administration. In the rat, a 14 day continuous intravenous infusion achieved the maximum exposures. The systemic, no adverse effect level in the rat was 660 microgram hour per mil from a dose of 232 milligrams per kilogram per day. This level was established due to a reversible renal finding and it is over 1,300-fold higher than the typical human systemic exposure following the approved inhaled dose of zanamivir of 10 milligrams twice daily. Rats were intravenously dosed greater than 800 milligrams per kilogram per day and within these animal studies, there were no dose

limiting toxicities due to CNS effects or treatment-related signs indicating that zanamivir affects behavior.

The pharmacokinetic characteristics of zanamivir have been studied in both humans and animals. In humans, most of the drug is deposited in the oropharynx and lungs. Because of poor oral bioavailability, only four to 17 percent of the inhaled dose appears in the systemic circulation.

There are no data directly measuring zanamivir exposure in the central nervous system of humans. However, whole body autoradiography has been performed in rats that received 10 milligrams of zanamivir intravenously. In this study, no, or the lowest detectable radioactivity was observed in the brain. Because zanamivir is a highly polar molecule, it is extremely unlikely that there would be substantial penetration of the blood-brain barrier into the CNS.

Based on the pharmacokinetic

characteristics of zanamivir including poor oral bioavailability, preclinical evidence of minimal CNS exposure and unlikely penetration of the blood-brain barrier, the estimated central nervous system exposure in humans is essentially none. Therefore, it is extremely improbable that inhaled zanamivir could result in a direct toxic effect within the central nervous system.

Within the clinical development program for inhaled zanamivir, there were four Phase III studies, that included children between five and 12 years old. The safety data from these trials reflect that the adverse events observed in children were similar to those observed in adults. The frequency of AEs and SAEs in the zanamivir groups were similar to that observed in the placebo groups. Within this clinical program, no abnormal trends in clinical chemistries or hematology was noted and no deaths were reported.

The major clinical trials of zanamivir were interrogated for neuropsychiatric adverse events. These clinical studies included all GSK Phase II and Phase III centrally sponsored study, one pediatric study conducted in Germany and all clinical trials conducted within Japan. For the clinical studies outside Japan, over 14,000 subjects were enrolled with more than 8,000 receiving zanamivir. For the Japanese clinical trials, over 1,000 subject were enrolled with almost 700 receiving zanamivir. All relevant adverse event terms within the neurology and psychiatry body systems were collected.

For the studies outside of Japan, 76 subjects reported a total of 83 neuropsychiatric adverse events. The events reported from the zanamivir receiving groups were similar to those reported from the control groups. For the placebo controlled trials, depressive and mood disorders

contained the most commonly reported events. For the rimantadine controlled trials, confusion and depressive disorders contained the most commonly reported events. There was not an increase incidence of neuropsychiatric events comparing the zanamivir groups to the control groups and no causal association for zanamivir was evident.

The initial analyses of these clinical trials data was completed by GSK in 2005. Interactions with the FDA concerning the more recent events reported from Japan prompted the FDA to provide a list of preferred neuropsychiatric AE terms according to the MedDRA dictionary.

For the clinical trials outside of Japan, the AEs were searched using this updated list of terms. The same conclusion resulted that this analysis did not reveal any evidence of a causal relationship between zanamivir and the identified neuropsychiatric events. For the Japanese trials, the

neuropsychiatric events collected were similar comparing zanamivir to the control groups. There were no AEs of suicide or suggestive of suicide or self-harm.

The serious adverse events in the GSK global safety database were also reviewed. This encompassed all the SAEs reports from subjects receiving zanamivir within GSK's sponsored clinical trials from the beginning of clinical development up to October of this year.

The SAEs were compared to the FDA provided list of AE terms of interest. This comparison yielded 12 cases which are described in Appendix C of the background document we provided. The cases were equally split between males and females and the subjects ranged in age from 19 days to 97 years. However, all but two subjects were adults, 23 years or older. Three events were injuries and nine events were neuropsychiatric events.

All 12 cases were considered not related to the study drug by the principal investigator and none suggested a causal association for zanamivir. In fact, for most cases, a clear alternative explanation was identified or the sequence of events was considered unrelated to zanamivir.

As part of our Japanese post approval commitment for Relenza, GSK is conducting three drug utilization investigations in Japan. The first investigated the treatment of influenza infection and was completed in 2002. There are two ongoing investigations, one investigating the treatment of influenza infection in children and adolescents and one investigating the emergence of drug-resistant influenza virus in children and adolescents treated with zanamivir. As part of this safety review, all three drug utilization investigations were reviewed for any reports of neuropsychiatric events which we'll describe here.

In the treatment of influenza investigation, over 4,000 subjects infected with influenza including approximately 500 children were enrolled. There were no suicides, suicidal ideations or jumps or falls reported. The most frequent CNS adverse events reported were dysgeusia, hypogeusia and sedation. No emerging signal for neuropsychiatric events was noted.

The pediatric treatment investigation is to span two influenza seasons from December 2006 to April 2008. The first 250 children were enrolled during this past influenza season and no neuropsychiatric adverse events have been reported.

The investigation for the emergence of drug resistance is planned to span three influenza seasons from December 2006 to April 2009. So far, 100 cases have been enrolled with no adverse events reported.

In order to supplement our internal data, we conducted a search of the literature

available through PubMed using the search terms "Relenza" and "zanamivir." Over 500 citations or abstracts were retrieved. However, no salient information addressing a relationship between zanamivir and neuropsychiatric adverse events was recovered.

In addition to this literature search, we examined the epidemiology of influenza-associated neuropsychiatric events. The most common neurologic manifestation of influenza are encephalitis and encephalopathy, both of which can be accompanied by seizure. Other described neurologic complications of influenza infection are listed here. These data suggest that the neuropsychiatric events observed during zanamivir treatment of influenza infection may be attributable to the infection itself.

The epidemiology of influenza-associated neurologic complications is slightly different in Japan as encephalopathy is a more frequently recognized serious

complication with an increasing incidence reported since the 1994-1995 influenza season. As Dr. Okabe described so nicely this morning, this complication is seen more frequently in children with a fatality rate as high as 30 percent in untreated cases. This syndrome typically presents with a rapid onset of high fever, seizure and progressive coma. Delirium and hallucinations have also been observed. Because of this, clinicians in Japan might be more aware of and astute in reporting neuropsychiatric events associated with influenza infection.

A comprehensive review of the GSK global safety database was undertaken as part of this review. This database includes all spontaneous and post marketing surveillance events reported to GSK and all unblinded serious adverse events from clinical trials. For the 2006-2007 influenza season, the review included all reports containing at least one event in the MedDRA system organ classes,

nervous system disorders, psychiatric disorders and injury.

From this last influenza season, 145 reports with at least one nervous system or psychiatric disorder were retrieved. All occurred after January 2007 with peak reporting between March and April. Of note this peak coincided with the timing of a pediatric adolescent safety alert issued by the Japanese Ministry of Health, Labor and Welfare. All of these 145 spontaneous reports were issued from Japan.

In the majority of these reports, zanamivir was prescribed for the treatment of influenza as opposed to its prophylaxis. The male to female ratio was roughly two to one. Ninety-nine percent of the cases were in children from six to 14 years of age. Of note, in previous years, most of the spontaneously-reported events were in adults with a median age of 44 years. The most frequency reported events during this last

influenza season are listed here. We conducted a careful review of these cases through a causality assessment which we'll describe next.

Within this causal assessment, we considered several factors, whether the time frame of events was consistent with a causative drug effect, whether the neuropsychiatric events were resolved despite continuation of zanamivir treatment, whether the neuropsychiatric diagnosis was confirmed or consistent with the reported events, whether the natural history of influenza infection and fever were more likely to have caused the reported event and whether concurrent medications or clinical findings were more likely to have caused the neuropsychiatric event. In addition, we assessed whether the information received by GSK provided evidence of a causal role for zanamivir or sufficiently documented the event regardless of the presence of an alternative

explanation. As you can see here, this last category represents 29 of the cases of the 145 reports.

The totality of this assessment failed to provide conclusive evidence of a causal role for zanamivir in these 145 reports.

The GSK global safety database including events reported prior to the 2006-2007 influenza season was also reviewed for this safety report. This review included all reports and clinical trial SAEs received by GSK from registration through the end of September 2006 identified by the FDA provided list of AE terms of interest from the MedDRA dictionary. This review identified 119 reports containing at least one term of interest.

Of these reports, most were reported from the United States. Japan, Canada and Germany also issued a significant proportion of the total reports. The male to female ratio was approximately two to one and the

ages of the cases ranged from 10 to 97 years of age with a median age of 44. Only 12 percent of the reports were in pediatric or adolescent subjects. This reporting profile differs significantly from what was observed during the 2006-2007 influenza season where the cases were reported exclusively from Japan and 99 percent of the cases were in pediatric or adolescent subjects.

For these reports prior to the last influenza season, the most frequently reported neuropsychiatric events are listed here. These AE reports also were subjected to a causality assessment. Again, this causality assessment did not reveal conclusive evidence of a role of zanamivir in these reported events.

Let me summarize the data encompassed within this review. The preclinical animal studies reveal no neuropsychiatric or behavior changes. Radio-label animal studies demonstrate minimal penetration of zanamivir

into the brain. Zanamivir has been tested in vitro in a PGP model and it had very low permeability and was not effluxed by PGP in an MDR1 MDCK2 cell.

The physiochemical and pharmacokinetic characteristics of zanamivir indicate that significant human CNS exposure is unlikely and a mechanism of direct CNS toxicity is highly improbable. Within the clinical trials reviewed here, there was no increased incidence of neuropsychiatric events in subjects who received zanamivir and no evidence of any causal association between zanamivir and serious adverse events. No neuropsychiatric events have been observed in the three Japanese drug utilization investigations to date.

There are no neurological manifestations of influenza infection that include encephalitis, encephalopathy, confusion, seizures and psychosis. These manifestations particularly encephalopathy are

more readily recognized in Japan. The cluster of neuropsychiatric AEs reported in the spring of 2007 all originated from Japan. This cluster of reports coincided temporally with a Japanese safety alert by the Ministry of Health, Labor and Welfare. Almost all of these reports were in pediatric patients. Many were transient and resolved while zanamivir treatment continued. No suicides, jumps or falls were noted.

Prior to the 2006-2007 influenza season the spontaneous neuropsychiatric reports received by GSK differed in that they were reported from multiple countries with a nonspecific clinical pattern and within a predominantly adult population.

Finally, the analysis of the GSK global safety database encompassing all available data through the most recent influenza season provided no convincing evidence of a causal association between zanamivir and the observed neuropsychiatric

adverse events.

We have concluded an exhaustive review and analysis of this body of information. We conclude that there is no evidence of a causal association between zanamivir and adverse neuropsychiatric events. The Relenza U.S. prescribing information accurately reflects the safety profile of zanamivir for inhalation and provides the appropriate level of guidance to prescribers. Therefore, no revisions or other measures are warranted at this time.

GSK will continue to monitor the situation closely for any emerging safety signal. Thank you.

CHAIRPERSON RAPPLEY: Thank you very much. In the interest of keeping us on time and getting us out on time, might I suggest that if people need to take a break they can just excuse themselves and do that and we'll continue. Is that acceptable to the group or would you rather take a formal break?

(No verbal response.)

CHAIRPERSON RAPPLEY: Keep going. Okay. I see nods and sort of equivocations. So we'll keep going. Open for clarifying questions. Thank you. Dr. Havens was first.

DR. HAVENS: Thank you very much for such a clear presentation. I was particularly impressed with the causality slides, A23 and A26, and I'm interested in the criteria with which you were so clearly able to decide that pyrexia and influenza were more likely to have caused the events in those two groups since that seems to have been a focus of a great deal of discussion today about which group members here have been less clear. So if you could describe to me the exact criteria that allowed for such great clarity it would be helpful.

MS. NUNCASHIN: I'll turn this over to my safety colleague, Dr. Rotin.

DR. ROTIN: Good afternoon. Rafaela Rotin. You pointed out very well that it is

not clear exactly what the definite criteria are for influenza as we heard during the whole day. However, mainly these cases we're reporting pyrexia, concurrent pyrexia, and the few cases where we assessed influenza is more probably related to the events described where mostly sick children being aggressive with their brothers and sisters in nonserious reports where the criteria of assessment of the spontaneous reports. I have to say also that here in this list the figures and the numbers described all one pair report but in one report there could have been many criteria which led us to find that there was inconclusive evidence for causal association with the drug and this was how we assessed the reports. Does this answer your question?

DR. HAVENS: It would suggest that if there was a potentially competing factor, if fever or influenza existed in the context of somebody who got zanamivir, then the alternative explanation might have been chosen

as opposed to the drug and that's what I understand you to be saying, sort of. I think we're not going to come to resolution.

MS. NUNCASHIN: That's accurate. If there was reasonable temporal relationship between the behavioral event and a documented fever the assumption was it was more likely related to fever than to drug. Is that accurate, Rafaela?

DR. ROTIN: Yes, it is. Yes.

CHAIRPERSON RAPPLEY: Dr. Ward.

DR. WARD: That was my issue as well.

CHAIRPERSON RAPPLEY: And I had the same question and I think that also is relevant for concurrent drugs administered as well as lack of another sufficient explanation. I think these are things we've been discussing all day and some of us have interpreted that as it's still possible it may be an association with the drug where you have concluded that it's not likely to be associated. So I think I see that difference.

MS. NUNCASHIN: If I could just respond. I think that sums it up quite well. I'll just point out to the Committee that as we were doing this assessment it was with an eye for convincing evidence of a causal association not with an eye towards clear evidence that it is not zanamivir. Am I clear?

CHAIRPERSON RAPPLEY: Yes. You wanted categorical evidence that the drug caused the abnormal behavior that was reported. And we've spend all day talking about --

MS. NUNCASHIN: Convincing, categorical, something along those lines, yes. Thank you.

CHAIRPERSON RAPPLEY: Yes. Mike.

DR. FANT: I have a couple of questions related to the point you were making about CNS distribution and you mentioned some data where I guess some rats were given the drug systemically and the radioactivity was monitored and you mentioned that "the lowest

area of distribution was in the brain." I was wondering if you could be more specific in terms of amount as opposed to just the relative amount relative to the other areas of distribution and what form that radioactivity, if you knew what form that radioactivity was in. And the second question is since zanamivir is inhaled and the data that you have is based on appropriately inhaled drug versus systemically administered drug. One question, what would happen if some of the drug made its way to the nasopharynx? Would it have increased access to the CNS?

MS. NUNCASHIN: Okay. I must not have been clear enough in my -- If we can put that slide up, please. In addressing the whole body radiography in the rat, I did not mean that the brain was the tissue in which the lowest amount was detected. I meant that the lowest detectable amount by the assay or none was detected in the brain and I believe the details of that study were submitted to

the FDA. I don't think they were included in the background.

Because we know that zanamivir has very poor oral bioavailability I would not expect significant mucosal penetration from the nasopharynx either. In addition to support the development of the inhaled formulation in terms of safety, we have administered high intravenous doses of zanamivir, as high as 600 milligrams twice daily to humans, and in those studies no neuropsychiatric or behavioral adverse events of this type were noted. Does that help you?

DR. FANT: Yes. I understand your answer. I guess there is no experimental -- I understand the answer that you would not expect certain types of absorption but is there any experimental data one way or another?

MS. NUNCASHIN: There are human data administering intranasal solution to humans. There are no data from those studies where we

tagged the zanamivir and looked at the distribution from that administration.

CHAIRPERSON RAPPLEY: Dr. Rosenthal.

MS. NUNCASHIN: I'm sorry. Go ahead.

DR. ROSENTHAL: I'm going to go back to the two slides 23 and 26, the causal analysis and I may not be understanding the way that you did this. But this morning we heard that around 50 percent of abnormal behaviors were observed before administration of Tamiflu and on the two slides that you present, it looks like only about two percent of subjects identified had their neurologic symptoms occur before the administration of the dose. Is that a correct interpretation?

MS. NUNCASHIN: Yes, as far as these reports.

DR. ROSENTHAL: So with zanamivir it seems like virtually all of the neurological events occurred after administration of a dose.

MS. NUNCASHIN: I'm happy for Rafaela

to take that.

DR. ROTIN: Yes. I can confirm that in the adverse event reports received the administration of zanamivir was in the vast majority of the cases prior to the events described.

CHAIRPERSON RAPPLEY: Other questions?

DR. MURPHY: I just want to go back to slide A6 and just clarify because I want to make sure I understand it. The animal tox studies, these were the routine animal tox studies. These weren't additional studies that were done, I mean, when you submit your application. It's what it looks like. I'm just verifying.

MS. NUNCASHIN: You're correct. This was part of the routine preclinical package to support any registration.

DR. MURPHY: Okay. Thank you.

DR. WARD: On the same slide, you mention that there was no dose limiting

neurologic toxicity. What toxicity was observed at the extremely high doses?

MS. NUNCASHIN: Could you put that up. The NOAEL was established in the rat. There were actually in similar studies in the dog a 14 day continuous IV administration, there were no adverse findings to establish a NOAEL. The finding that established the, you can put that up, NOAEL at 660 microgram hr/ml was a reversible vaculization of the proximal renal tubule within the cortex that in another study in a recovery phase went away with the withdrawal of the drug. But rats were dosed as high as 864 milligrams per kilogram per day and did not exhibit any sort of behavioral signs that would indicated a CNS sort of behavioral effect.

CHAIRPERSON RAPPLEY: Dr. Daum.

DR. DAUM: And on that same note, can you tell us a little bit about how you look for behavioral signs in a rat, seriously, that are indicative of neuropsychiatric involvement

while you're continuously infusing something and how was that done?

MS. NUNCASHIN: My understanding is that's done by frequent time points at which the animals are observed and their behavior is charted and I don't know that -- it's not my area of expertise. So I don't know if there are scales or behavioral scoring scales. But I would imagine something to that effect.

CHAIRPERSON RAPPLEY: Other questions? Okay. Thank you very much.

MS. NUNCASHIN: Thank you.

CHAIRPERSON RAPPLEY: I think we'll move now to our wrap-up and conclusion and Dr. Lewis will provide that for us.

DR. LEWIS: Well, it has been a long day and we've heard a lot of information from a lot of different sources. I'll take just a few minutes to summarize what we've talked about.

So what we've covered today is some regulatory history for the drug we have

discussed, primarily Tamiflu, recaps of both the 2005 and 2006 Pediatric Advisory Committee meeting discussions and conclusions. Today we've had some perspectives from both the CDC, thanks to Dr. Shay's efforts to call in and from our colleague, Dr. Okabe from Japan.

We've reviewed the literature since our previous meetings and this has been supplemented by literature reviews both from Roche and from GSK and we've summarized some of the new data we've looked at including the health claims database studies submitted by Roche, additional preclinical and clinical studies found in the literature, clinical pharmacology and pharmacogenomics studies that might be relevant.

As the previous advisory committees had requested, we've tried to address the prophylaxis use of Tamiflu and I think what you should come away with is that both the FDA and Roche have attempted to identify cases of these events with the use of Tamiflu as

prophylaxis and it has been very, very difficult to identify any cases with the types of databases that we've had available to us. The few cases that the FDA identified were so confounded as to be uninterpretable and many of them appeared to have clinical flu as compared to non-flu prophylaxis.

We've reviewed other antiviral products for influenza and I think you've heard that we've identified these cases with all of the other products, but because of numbers and timing we see them more predominantly with Relenza and not so much with amantadine and rimantadine which are not in great usage these days.

We've updated the FDA safety review as requested for both pediatric deaths and predominantly neuropsychiatric events for Tamiflu and other antivirals using both MedDRA terms and some clinical characterizations that both we and Roche have used although slightly different systems and we presented you some of

the data that showed the differences in labeling between the U.S., Japan and the EMEA, the European agency.

In summary, I think it's fair to say that we continue to see reports of abnormal behavior in both pediatric and adult patients. These events are not fully explained by influenza associated encephalopathy or encephalitis. I think we've discussed that in some detail. These appear to be different processes. They may have some overlap, but there seem to be some that are clearly different.

We've been unable to definitively tease out whether this is related to the drug, the disease process or some combination of disease and drug and also whether this is in some way related to the population involved. I think that's still quite an interesting and unanswered question.

So our questions for the Committee are really all fairly similar and I'm just

going to read them and then we can come back and go through them with discussion later and you may want to discuss them in a slightly different way than we've laid them out.

The first question is based on the totality of data presented today on neuropsychiatric events and the possible relationship to oseltamivir, does the current labeling for oseltamivir adequately address the safety concerns regarding these neuropsychiatric events. If no, what other steps should be taken to ensure safe use of oseltamivir in the U.S., for instance, as was mentioned, labeling, risk communication, prescriber or patient education? And what I'd like for you to do as a committee is to not try to focus on specific wording of a labeling because there are many things that go into labeling requirements. But if you could come up with broad concepts or specific types of events that you think need to be included if you think anything else needs to be included.

That would be the most helpful.

We have basically the same question for zanamivir. I think we've heard for the first time this year that there have been reported cases that sound qualitatively quite similar and I would remind the Committee that when we first presented this information on Tamiflu two years ago and again last year, we had about the same amount of reports of neuropsych events in children on Tamiflu as we now have with reports of these events with Relenza.

Question number three, this is a very similar question related to the safety concerns related to amantadine and rimantadine. These are already labeled fairly significantly for neurologic events, but that labeling is certainly quite old and if you have concerns or suggestions about updating that, we would appreciate hearing about that.

Question number four, do you have any suggestions for other studies or analyses that

seem feasible that might clarify this safety issue?

And lastly, we are currently meeting on a monthly basis during influenza season to review all adverse events reported with the four influenza antiviral products. We plan to continue this through the current flu season and upcoming flu seasons. At this time, an update to future pediatric advisory committees is not planned. However, if important safety information emerges during our continued monitoring, we would certainly report back to the Committee and we'd like to know whether you agree with this approach.

I guess if we could go back to question one so that the Committee can see that while they're discussing.

CHAIRPERSON RAPPLEY: Okay. So we have five questions to address and we can do this two ways. We can either have it a time limited general discussion or we can begin with question number one. Does the Committee

feel they're ready to begin with question number one? I will take comments, indication of comments, or who would like to begin the discussion? Yes, Tom.

DR. NEWMAN: It would be helpful to actually have the labeling on the slide up there. I know it's been in a number of presentations, but I know I read some place there was going to be an addition of the words "some of them fatal." There have been serious behavioral disturbances and I just want to know if that's in there now or is that not in there?

CHAIRPERSON RAPPLEY: It's not in there. It's actually on slide nine.

DR. MURPHY: It's in your binder, the one that had this --

DR. NEWMAN: Which?

DR. MURPHY: At the very back is the label and that "fatal" was not in there.

DR. NEWMAN: So that was proposed someplace?

DR. MURPHY: Yes.

DR. NEWMAN: I know I read that someplace.

DR. MURPHY: That was proposed.

DR. NEWMAN: Okay.

DR. HAVENS: And just in this, it's also on page 28 in the bigger batch of stuff we got and then I don't know. Is what's on page 29 in this Rothstein compendium, is that the proposed language for the oseltamivir labeling listed below? Should we really believe that?

DR. ROTHSTEIN: That was proposed from our division from our review of the post marketing data. That's for consideration.

CHAIRPERSON RAPPLEY: That's what the staff suggest we consider.

DR. HAVENS: So page 28 and 29 are where you can find current and proposed in the Rothstein.

DR. ROTHSTEIN: Slide nine.

CHAIRPERSON RAPPLEY: Slide nine.

DR. ROTHSTEIN: Slide nine from my presentation has the current labeling in there.

CHAIRPERSON RAPPLEY: Yes, if we could find slide nine from Dr. Rothstein's presentation. That would give us the current label for oseltamivir and why don't we then begin with question one and discuss whether or not that labeling is adequate or if we suggest additional concepts or things that should be added. Yes, Dr. Havens.

DR. HAVENS: It seems to me looking at that current one and then the potential proposed new labeling the issues of deaths have been reported is one of the things that comes up. The discussion today suggested to me that I would like to see a very strong statement that these neuropsychiatric events have occurred in patients with influenza who are not treated with Tamiflu. That would stress the uncertainty and might help people begin to associate these transient

neuropsychiatric abnormalities with influenza itself and not just with its treatment. That might also change the recommendation for how long you would want to monitor someone in this setting, not just for the duration of treatment, but I would potentially leave that out altogether.

And then the other thing that came up, I think in the letter that we read was do we really want to say that if you have this problem, you should stop the drug. So that would be the third issue.

One, yes, you should put in that people have died from it. Two, I would make a strong statement that it's occurred with influenza without the drug and, three, would consider whether or not you want to, I'm less clear on that obviously, say if you have these neuropsychiatric events stop the drug. But that was one of the issues that came up.

CHAIRPERSON RAPPLEY: Okay. So we have suggestion of three concepts to add to

the labeling. One is the fact that it's been noted that there have been fatal outcomes from adverse events, two, that there's uncertainty because these outcomes have also been seen in those who have not taken the medication and, three, there should be language that says stop the drug if you have these symptoms.

MS. VINING: I would also like to suggest that there be some mention of the abrupt nature on the onset of these. It seems to me that a number of the reports had indicated that children are identifying these behaviors and abruptly taking some sort of an action whether it's running or falling or other issues.

CHAIRPERSON RAPPLEY: Abrupt meaning the behavior itself is sudden or abrupt or with the timeliness with taking the medication?

MS. VINING: Abrupt onset.

CHAIRPERSON RAPPLEY: Onset. Okay. Dr. Newman.

DR. NEWMAN: I agree with including the information that they can also happen not on Tamiflu, just from influenza. I think that's important. I guess one other concept which I'm always saying I know it's kind of a struggle, but the way it is now, the current labeling, it doesn't give any indication to the consumer at all about how rare these are and so it makes it very hard for them to know how frighten or scared to be about it. So the general concept of some indication of a possible rate, whatever it is, one in 100,000 or one in one million, to get some idea of how uncommon these fatal events are I think would be helpful.

CHAIRPERSON RAPPLEY: Dr. Kimberlin.

DR. KIMBERLIN: Along those lines, the question before us is does the current labeling for oseltamivir adequately address the safety concerns for neuropsychiatric events and I'll say in my opinion I think it overly states the safety concerns. I just

don't see in the data presented today the causation. I don't see the data that says this is oseltamivir related. Rather I see data that I think much more strongly suggests that it's influenza-related which I think is why the original suggestion to add that was in there.

But perhaps the other way to do it is to either not change anything, just leave it as is so it doesn't open it up for additional negotiations as was said takes place when the label is considered to be changed, or maybe even more radically just go back to the label as it was before a year ago where this wasn't in there because again to have it in the label to me implies that we have a pretty good belief that this is related to the drug and I personally don't see it.

DR. MURPHY: I just want to make one thing clear is that we don't have to have causality to put it in the label. But I mean that's fine. I think just if you think that

it's overstated, that's a perfectly great opinion and we want to hear that. But I just wanted to make sure that people on the Committee know that we don't have to proved casualty for it to go in the label. You know the label will have lots of things that occurred during trials that we're not saying the drug caused. So it's how do we make clear what the risk is or is not.

DR. KIMBERLIN: And I appreciate that. I guess I would think that if it's in the label that people are going to look to it as being related to the drug in some form or fashion, a layperson especially, but I would say even physicians who are in busy practices. So I think while it doesn't have to be I'm sure from a regulatory or a legal side, it implies that in fact there is an association especially if we keep adding more to the statement as compared to either as I said leaving it as it is or perhaps even rolling it back to where it was a year ago.

CHAIRPERSON RAPPLEY: Dr. Bier.

DR. BIER: You know, I also support the statement adding something about the presence of these symptoms in the absence of the taking the drug because I was convinced like some of the people that have just spoken that the causality is likely to be influenza. But if that's the case in most instances where you have a complication when someone is taking a drug, the default position is to stop the drug. But if in fact influenza is the cause here, might that not actually be the harmful decision to take?

CHAIRPERSON RAPPLEY: Dr. Hudson.

DR. HUDSON: I think the components in the label that have been stated are actually good to start, but maybe should be more generic, initially stating something to the fact that a variety of neuropsychiatric effects or behavioral effects have been observed in association with influenza and then go to Tamiflu and then that statement

that we have already, the relative contribution of the drug to these events is not known or how that is interacting, how the drug is interacting with the disease. If that can be emphasized to start generically with the variety of neuropsychiatric effects and then put the rarely for the delirium and the fatal events, somehow give the issue of how uncommon or rare these are.

DR. KOCIS: I want to reflect back a year ago to my first meeting here when we first reviewed Tamiflu, one year after pediatric exclusivity. I was new to the meeting. I didn't say much. I just listened to what comments were said and one of the committee members who is not here who I won't name, he was outraged that we didn't take a stronger stance about these deaths, suicidal deaths at the time, knowing we have very, very limited data, certainly no causality at all and it came back to the balance of risk and benefit.

And when we come back to that my comments will reflect upon that. What we're saying is when we give Tamiflu to children who have influenza, we shorten by one day or a day and a half their symptoms. We're not stopping the course of the disease. We're not stopping a 30 percent mortality rate from an encephalopathy or whatever that is. We are shortening symptoms by one day.

So the benefit to me is relatively minor and I would say probably for myself and my children I don't expose or I wouldn't expose them to use of a drug like this to shorten symptoms of influenza by one day. But certainly other people feel differently and that's their right and the drug is effective at doing that and I think that that's important.

But when we balance that with the risk, then I think that's where I come back to the label and what we need to say in that is the risk needs to state that this is, one,

rare. Any number we look at, everything we've been talking about, it's extremely rare. Call it idiosyncratic. Is it related to the drug? We know that if you take the drug and you don't have influenza you don't have these reactions. You know if you take the drug prophylactically you don't have these reactions.

We know children have fever all the time and we've seen that for generations. They don't jump out windows. We see children with influenza for decades before these drugs came on the market. These things weren't known and we had tall buildings at the time and maybe we're just picking up on that now and maybe that's true and maybe we're just going to start recording all of these things.

But I think it's important in the label that we say this is rare, that the potential -- the events include self-injury including death because self-injury to me is you cut yourself, you slam your head, you put

your hand in the door or something along that level of injury. I think it needs to include that.

The role, if any, I wouldn't even say the relative contribution of the drug because we can associate that through all the stuff that we've heard today, at least, I can. So I would include the role, if any, is related to the drug and that no events have been documented in patients using Tamiflu prophylaxis to again point out we haven't shown causality.

I agree, I would not stop the drug if this is related to influenza. I think there are a lot of decisions that go into treatment of patients with drugs and I wouldn't stop them. I think we mentioned this last year and included a call to your doctor and help make an informed decision about that.

The abrupt sudden nature we brought up and I think that's an important thing, early on in the course, so you can be

observant early on in the course of influenza with or without treatment with the drug. And those were my comments. Thank you.

CHAIRPERSON RAPPLEY: Dr. Ward.

DR. WARD: I would just like to separate kids with fevers and kids with influenza. Thousands of people die from influenza each year and I think the encephalopathy and encephalitis that is described in these children is different and I think it is more severe and I think it does relate to some of these bizarre behaviors that lead to injuring themselves and I think to the extent that we have uncertainty and we have a drug that may be beneficial we've not talked about reductions of mortality. We've not talked about really benefits of therapy to that degree. We've really focused on the adverse events. So I want to maintain the uncertainty that's been expressed by others in this label.

CHAIRPERSON RAPPLEY: But I think in

one of our reviews they do review the benefit. There's literature about the benefit of the medication and the conclusion that I came away with is that it does shorten the number of days in which one has symptoms. Now whether it has other more beneficial effect is open to debate. Some studies say yes. Some say no. Some studies I've critiqued that show in either direction. But the strongest evidence was that for shortening the days of symptoms.

DR. WARD: Okay.

CHAIRPERSON RAPPLEY: Dr. Newman.

DR. NEWMAN: Yes. In terms of another category of things to add to the label, I think this is really a case where the system worked. We asked for more information for a couple years and one year ago and I think we really got it today.

CHAIRPERSON RAPPLEY: We got 66 documents.

DR. NEWMAN: I feel much better informed about this and actually quite a bit

reassured and I wonder if some of that information can go in the label as well, the information from the claims data and from the general practice database in the U.K. and the careful analysis of all the clinical trials. Those, I think, all address this question. So some of the other categories of data that were reassuring that we've heard today I think would be helpful to put in the label as well.

CHAIRPERSON RAPPLEY: Dr. Hall.

DR. HALL: I would first of all like to support what Melissa said in terms of the format of this for starting out with the influenza does cause a certain amount of abnormal responses. But neuropsychiatric events also is a precise part of that. But it would be helpful if it gave some kind of incidence there so you have some relative idea of the background for influenza alone and then going through that this is also been reported with Tamiflu and it's possible some kind of relative incidence of that but it should be

very, very small.

My concern is particularly the last thing, patients with influenza should be closely monitored for signs of abnormal behavior throughout the treatment period, for two reasons. One is I can see that being not feasible and, two, that most children who have influenza, as a parent, you cannot watch them closely and what does that really mean? And secondly, that most children in this country in contrast perhaps to Japan do not get the diagnosis of influenza. Flu is used in nonspecific way and as we're recently shown the actual diagnosis of flu on a population based study is relatively rarely diagnosed by physicians even in those that are hospitalized. So that last statement I find to be particularly difficult and would voice for not having it here. Thank you.

CHAIRPERSON RAPPLEY: Dr. Cnaan.

DR. CNAAN: Yes. First, I also would like to support the sequencing suggested by

Dr. Hudson because it just would be easier to read and to understand from a parent perspective.

The second thing that I wanted to go back to is the tall buildings comment that it preceded Tamiflu. That is true but we don't really have a good system of surveillance of kids falling from tall buildings if there isn't a medication involved. So we really don't know and yesterday we saw some more than we ever saw before but it is reasonably likely that these events have been going on with influenza for dozens of years. We just don't know how much.

So I think therefore the risk/benefit is really tricky because it might that by shortening by a day or a day and a half which is the only defensible benefit at this point it might be preventing some cases of neuropsychiatric outcomes. We don't know. I don't know that we can study it at this point in the game. But I would just make very sure

to be as inconclusive as the data really are.

CHAIRPERSON RAPPLEY: Or as honest about that uncertainty.

DR. CNAAN: Yes. Dr. Kimberlin.

DR. KIMBERLIN: I guess the idea of adding what I think are the more definitive data that we saw today to the label, mainly influenza itself, the disease itself, didn't have associated rare neuropsychiatric outcomes or events is the more reasonable of the things I'm hearing from my perspective.

But I still feel that if we then go on to discuss oseltamivir the implication then is that some of it is due to oseltamivir despite language that might say we don't know for sure, but death occurs. People are going to hear "death" and I think that if a statement is made about it, perhaps from my standpoint again leaving it as the more general statement that influenza can cause these sorts of things and it might be worth watching for that even perhaps, would be

reasonable but could then go on to a specific antiviral drug when we don't have the data in my opinion to suggest causality and we've asked for those data in other things and they've delivered them and they don't suggest causality, I think is allowing an overstatement to be maintained and that concerns me somewhat.

CHAIRPERSON RAPPLEY: Could I ask our Patient Representative her thoughts on that, this kind of language in a product insert and just sort of need to know and who makes the judgment?

MS. CELENTO: I feel that for the most part people don't actually read a lot of what's going to be included and it's really the practitioner who can make the difference in terms of conveying some of the information and giving some cautionary statements. So I'm not quite certain the labeling product inserts versus practitioner conveying the information to a parent, I'm not certain which one is the

most appropriate. But I feel that giving people caution and making them aware that they should be monitoring their child is important because their child is sick. Whether it's the flu or the drug that is creating the situation, the child really should be monitored.

CHAIRPERSON RAPPLEY: Dr. Daum.

DR. DAUM: So I find this not easy, I must say, and I guess the first thing I wanted to just comment on something we passed by real quick which is that we have information that the drug can be exonerated somewhat because it doesn't cause the problems in a prophylactic use sense and I didn't see enough data to say that, I must say. I would have loved to have seen more and I would love to have that as a take home but I really didn't come away convinced from what I saw that that's the case. Too few patients, not that there was a problem.

The second thing that I wanted to

comment on though is I'd like to suggest that we consider together whether the language that was put into the insert in November `06, not very long ago really, is inappropriate and needs to be changed because the very act of changing it seems to me is a signal that there's something wrong or we have a new belief about what was put in there.

There have been many suggestions for what kinds of changes should be made and perhaps they all should be made. But in reading it over, it doesn't offend me. It says some things that are true. It says there have been some reports, mostly from Japan. The reports are mostly among children. The contribution of the drug isn't known. And people with flu should be monitored.

So I guess this is 10 or 11 months old, this change, and did we really hear something definitive enough today to modify that statement and signal to the practicing world, I'll take your point, the packet insert

reading world, that something has changed and I'm reassured by most of what I saw today. I also think the system worked. I don't have any stronger belief than I did before that there's a problem here.

But I'm not quite what's contributing to what. My own take home is that influenza can cause bizarre behaviors and influenza treated with Tamiflu can cause bizarre behaviors and I'm not sure whether there's a contributing factor or not. But my guess is there probably isn't. But the statement in November `06 doesn't say there is. I guess it's a little bit of an argument for not rocking the boat too hard based on what we've seen today.

CHAIRPERSON RAPPLEY: Dr. Fant.

DR. FANT: Yes. I would just like to respond to a couple of comments that have been made up to this point. I would be in favor of including in the label our ongoing uncertainty and that doesn't imply expressing causality or

leaving the impression of causality.

But one of the important functions of this agency that I've kind of gotten a sense over the last few years that the public really expects is to be made aware and I never hear anything from the public or at least on the public side in terms of getting too much information. The biggest complaints I tend to hear is not getting enough information and this question has been put before this committee for the last two to three years now and we're still uncertain. And if we're still wrestling with it, to me even though we don't have any definitive to put in the label yet, I think that that in and of itself says that we have enough concerns that it warrants conveying those concerns to the public.

And especially when it involves -- whether it has to do with the flu or it has to do with Tamiflu, it involves certain behaviors and activities that in either case the public, although they happen infrequently, may need to

more aware of and watch for more closely. So, in that sense, I wouldn't take out the wording that encourages people to monitor patients more closely throughout the duration because the one narrative that really sent chills up my spine was the little kid who came into the parents' room in the middle of the night and they thought he was dreaming until mom went to his room the next day and found the window open and footprints on the window sill and his feet were dirty and realized what he had communicated and they thought was a dream this actually probably happened and he probably came very close to a jump or whatever we would have called a jump or a suicide or an accident or whatever and he probably did it without even being awake or knowing that he was fully awake.

Now that's just one narrative, but all of them seem to sort of add up to very abrupt transient episodes that need to be watched. Now they don't happen frequently.

So when things don't happen frequently, anything that kind of elevates awareness is probably not a bad thing to have happen.

And finally at least in my own personal circle of contacts and friends and relatives and whatnot, these little inserts that you get with your drugs from the pharmacy now, I'm seeing more and more people who will read every word of them. Often times, they would just sort of go in the garbage with the receipts and whatnot, but I'm just seeing more and more situations where people are reading everything about that.

So making more information available to the public and to the patients and conveying this because they're going to be the first line observers, the parents, the spouses, the friends, in terms of monitoring for these things that we are talking about here. Whether we're keeping that in the label or even communicating that in the med sheet that the pharmacists prints out to give to the

patient to read.

CHAIRPERSON RAPPLEY: If I could summarize. I hear three suggestions, three positions, and if we can deal with the first two, we could move onto the third or not as needed.

The first, there was a suggestion not to change the label at all. There was a suggestion to go back to the previous label. And there is a suggestion to change the label and then in a variety of ways. Does somebody want to put a motion out to not change the label and we can take a vote?

DR. BIER: Yes. I move that we don't change the label.

CHAIRPERSON RAPPLEY: Any second?

PARTICIPANT: I second that motion.

CHAIRPERSON RAPPLEY: Okay. Shall we vote individually? Okay. Would you like to start?

DR. BIER: I vote yes.

MS. CELENTO: I vote yes.

CHAIRPERSON RAPPLEY: Can I just restate? You are voting yes to not change the label.

DR. BIER: Yes, to not changing the label.

CHAIRPERSON RAPPLEY: Correct. Yes. Keep the label the same. Thank you.

DR. CNAAN: Agreed to keep the label the same.

DR. DAUM: Yes.

CHAIRPERSON RAPPLEY: Dr. Fant, you're thinking.

DR. FANT: Well, yes. Technically, my answer is a no, but my suggested change would be relatively minor.

CHAIRPERSON RAPPLEY: Right. So if we decide to change the label, then we'll come back and discuss what we should change, what elements we would want to emphasize in a change. So if the vote ends up being not to change the label, we don't need to visit that. Does that make sense?

DR. FANT: Okay.

DR. NEWMAN: And we're talking about the whole label, not just this little precaution section.

CHAIRPERSON RAPPLEY: Yes. Carlos suggested everybody vote at one time by raising the hand. Dianne.

DR. MURPHY: Well, I think if people want to say something, that's why if we can go around and make it very brief.

DR. PENA: Right. I think they can. I just think that we should actually get on the table who is voting how and then if additional comments want to be made they can.

CHAIRPERSON RAPPLEY: Okay.

DR. BIER: Can I -- As the one who made the motion, I said the word "label" but I meant the precautionary statement. So this label contains other information that we haven't discussed. So that wasn't the motion I intended.

CHAIRPERSON RAPPLEY: But the

question put to the Committee is in regard to this portion of the label. Is that correct? We are not asked to revisit the entire package insert.

DR. MURPHY: Yes, that's correct. We're talking about this specific part of the labeling.

CHAIRPERSON RAPPLEY: Yes.

DR. CNAAN: My question is how do we deal with Dr. Newman's comment that said please add some of the information from the day to other parts of the label.

CHAIRPERSON RAPPLEY: That would be a change. Okay. So let's be real clear. If we vote as a group that we do not want to change the label, it stays as is, no additions, no deletions.

If we want to add things to this label, if we want to convey to the agency that there are concepts we want them to add, then we need to vote to change the label and discuss what those concepts should be.

DR. KIMBERLIN: So may I -- So it sounds like we're voting to either change the label -- Well, we're voting to not change the label or we're voting to change the label and if we vote to change the label, then things can be taken out or added in.

CHAIRPERSON RAPPLEY: Correct. Dianne, did you want to say something?

DR. MURPHY: Well, I was just going to say if the majority of the Committee voted not to change the label I think we would still want to make sure or have you summarize what others in the minority. We would like to have a minority opinion of what things the minority would want to have changed. So it's a very good way to do it. Find out who doesn't want to change it, get that and then hear from the whatever it turns out to be. But just in case it was the majority don't want to change it, I think we should still get some comment from the minority.

CHAIRPERSON RAPPLEY: Okay. I'm

sorry. What?

DR. PENA: Vote all at once.

CHAIRPERSON RAPPLEY: Vote all at once. Okay. So is that agreeable to those who have already ventured out singly? Okay. Let's take a vote by hand show and this would be a vote to, yes, keep the label the same. No changes.

(Show of hands.)

CHAIRPERSON RAPPLEY: I see five votes to keep the label the same. And votes to change the label.

(Show of hands.)

CHAIRPERSON RAPPLEY: I see nine votes to change the label. I only vote if there's a tie. Is that correct? Is that what you counted?

DR. PENA: That's correct.

CHAIRPERSON RAPPLEY: And any abstentions?

(No response.)

CHAIRPERSON RAPPLEY: No abstentions.

So the Committee is voting to recommend a change in the label. Now let me summarize the things that were suggested be changed. There seems to be endorsement of a concept of discussing in a generic kind of flow first the problems with flu and then the problems with Tamiflu and then the uncertainty about the association of the medication with the symptoms of concern. There was strong endorsement of addressing the rate of occurrence of these unusual events or rarity of these events, the characteristics of these events, the abrupt nature, the result in fatality and need for monitoring. Were there others? And the need for monitoring was still kind of debated back and forth about whether or not that language should be strengthened. Yes, Dr. Havens and then Dr. Hall.

DR. HAVENS: The other two issues that came up were should we say that some people have died from this and should we recommend that the drug be stopped if such

neuropsychiatric events occur.

CHAIRPERSON RAPPLEY: Okay. So -- Go ahead. Did you have another thought?

DR. HAVENS: Yes, but I just wanted to add to your list because --

CHAIRPERSON RAPPLEY: Okay. You can list it.

DR. HAVENS: I want to talk later but only when it's my turn though.

CHAIRPERSON RAPPLEY: Okay. Thanks. Dr. Hall.

DR. HALL: I just wasn't clear in terms of the monitoring. It's not whether in or out, but you're including that it's just a slight rewording. To me, it should be more clear that you monitor patients with the influenza and not the other way around. The way it states now it seems to be the onus on the drug.

CHAIRPERSON RAPPLEY: Other things to add on the list and then we can go down the list and we can either have dialogue or we can

do a show of hands to see endorsement, not so much formal vote, but just so the agency has a sense of how strongly we feel about that. Yes, Dr. Havens.

DR. HAVENS: One issue that comes to mind as I've listened to the discussion is that we're really talking about two separate things. One is education of practitioners and the public about influenza itself which might best be put in something that's not in this precautions part of the label. And the other is specific language that we want to be precautionary about the use of the drug that would allow us to identify much of this discussion in a paragraph that might be separate from this specific precautions statement and still outline many of these issues like the potential for abrupt change in activity that could be dangerous, that people died from such activity. Some of the things that are in here serve an educational purpose and some serve a real precaution about use of

the drug purpose and it might be that there's more information now that would allow us to have a paragraph that was educational and really did present a lot of what happened somehow separate from the specifics of do this when you use this drug.

CHAIRPERSON RAPPLEY: Okay. So would it be safe to say that we would rely on the agency to find the proper place to insert those important concepts?

DR. HAVENS: I would feel very comfortable relying on the work of the agency and their interactions with the drug company to come to some agreement on that.

CHAIRPERSON RAPPLEY: So another issue -- So I'll restate the list and I'll just do it one at a time and then invite conversation or show of support for that. The discussion about the influenza was to indicate that these symptoms and the behaviors of concern and outcomes also occur with influenza as well as with the medication. Is there

anyone opposed to that concept?

(No hands.)

CHAIRPERSON RAPPLEY: And then the ambiguity that we feel or the uncertainty that we know at this point in time about causality. Is anyone opposed to that?

(No hands.)

DR. DAUM: And when you say that, it's difficult to participate in this conversation. So I'm asking for some guidance.

CHAIRPERSON RAPPLEY: Please talk. Go ahead. I'm sorry.

DR. DAUM: I don't think there should be a change. So now you're proposing changes that I have to sort of agree or disagree with and it's hard because I don't think there should be any change. It already says --

CHAIRPERSON RAPPLEY: That would be the minority opinion though.

DR. DAUM: Well, a substantial minority though.

CHAIRPERSON RAPPLEY: Right, and we want to flesh that out so that it can be submitted as such.

DR. DAUM: And the statement already says that the relative contribution of the drug to these events is not known. So when you say that we don't know about causality, what are you proposing?

DR. HAVENS: But the way it's stated under -- does it give enough strength to what's come through today which is that there's actually a high likelihood that some of this is from influenza itself. Maybe not as much clarity about causality as some of our pharmaceutical colleagues had but still a little more than maybe we had last week. So it would just highlight that we potentially felt more strongly. This says nothing.

DR. DAUM: Exactly. That's why I like it.

DR. HAVENS: That's fair. But I would rather say "could be from the flu."

DR. DAUM: What about putting that -- what about negotiating on that point? What about adding a sentence saying "influenza can cause the same neurologic problems."

CHAIRPERSON RAPPLEY: I think we did say --

DR. DAUM: I would be comfortable with that.

DR. HAVENS: Yes, and I would separate that maybe into a paragraph that specifically talks about neuropsychiatric events and then let the FDA and the companies negotiate what's going to be in the precautions part of this specifically because that may be a little trickier.

DR. DAUM: Now the last sentence --

DR. HAVENS: The other approach to this would be to take, as has been raised earlier, a more public health notification approach and educate people through the CDC or whatever organization wants to do that to say these are things to look for when your kid has

the flu and put that stuff in and that would I bet dramatically increase reporting but then you would have set up a reporting structure that could take those reports outside of the FDA.

CHAIRPERSON RAPPLEY: We're still on question one and it's close to 5:00 p.m. and I'm not certain that we're really that far away on many of these things and really at this point we're not writing language for you and we're just suggesting additional concepts that might be included. Can I ask the staff --

DR. LEWIS: All of these concepts that have been discussed are very helpful and things that the representatives from the sponsors are here and are also hearing this discussion. So that certainly makes any of our negotiations about labeling easier.

DR. MURPHY: I guess the only thing we would say because I think instead of going through each one of these unless you guys want

to go home tomorrow, having a discussion about each one of them because you listed the topics, is if somebody has just a burning need to list another topic that was not brought up because I think we've gotten the four or five down so far that we would take that and move forward with that.

CHAIRPERSON RAPPLEY: Yes, Dr. Kimberlin.

DR. KIMBERLIN: And I kind of had the same discomforting feeling about having not voted initially to not change the label. But if it is being opened up what I'm hearing is and if it is to be changed I would be more in agreement with is to put the emphasis on influenza and influenza-related symptoms and actually then to not just add that but actually takes away the emphasis of Tamiflu or, at the very least, broaden the emphasis to antiviral therapy as a whole as compared to one drug receiving such the bull's eye focus of this. If we focus more on influenza, what

I'm hearing around the table is what people I think would be in agreement with.

That's different than the wording that was initially proposed where it was aggressive in terms of fatalities associated with this, rather it's putting the emphasis more on the disease process itself.

CHAIRPERSON RAPPLEY: Dr. Hudson and then Dr. Kocis.

DR. HUDSON: I have another comment that relates to one of the other suggestions and that's withdrawal of the drug because I think that's completely different. I think we need to vote about that because that has major medical/legal implications for physicians who are prescribing these medications and all of us may not agree with that.

CHAIRPERSON RAPPLEY: Dr. Kocis.

DR. KOCIS: Yes. Again I don't think we're too far off and I don't disagree with anything. I don't find any compelling information that we've learned today that

would say this is related to the drug. I think we've gathered more information, new information. I think we can make a better label now having heard and learned from what we did the first time, the first time I did it in `06 and just throwing that one caveat, the relative contribution of the drug, I would pull that out and add "the role, if any" because you're saying there's a relative contribution which infers that there is some contribution be it small, medium or large and I certainly don't hear anything to convince me of that and I think we just need to keep collecting data and come back in another year or two and review things and hopefully we'll learn more.

But I think we can do a better more accurate label than this and I don't think we should exclude death because those are the reports. The reports were children died with influenza who were also taking this drug and I don't think we should hide that.

CHAIRPERSON RAPPLEY: Is anyone opposed to using the phrase "death" or using "death" in a phrase or "fatality" and allowing the agency to decide how to word that? Related to influenza and uncertainty about the relationship to the medication?

DR. FANT: Yes, the way the label is written now it seems like an easy place to do it is right after it says "self-injury, including death." And I think that accurately says what -- states the facts.

CHAIRPERSON RAPPLEY: Okay. They'll take that suggestion. I think I heard Dr. Hudson then suggest that we also individually consider this notion of whether we should change the language about stopping the drug and currently it says, "ask your doctor." Am I correct? If you have these symptoms, inform your doctor or ask your doctor.

DR. LEWIS: Actually, that's not currently in the label.

CHAIRPERSON RAPPLEY: There is no

reference to it at all.

DR. LEWIS: That's correct. It just says "to monitor closely during the period."

CHAIRPERSON RAPPLEY: Okay. So do I have a motion about that kind of language?

DR. HUDSON: I have a compromise.

CHAIRPERSON RAPPLEY: Go ahead.

DR. HUDSON: I think what could be stated is the benefits and risks of continuing antiviral therapy should be carefully evaluated if these symptoms develop in a given patient. It seems like you can't -- since we're not even attributing the drug to some of these reactions. So I could see that I would want to use it. These won't tie the physicians' hands if this is a really clinical indication and the benefits far outweigh the risk.

DR. DAUM: It's so much better than "ask your doctor." I like that a lot.

CHAIRPERSON RAPPLEY: Dr. Newman.

DR. NEWMAN: My problem as someone

who might be at the other end of this, I mean, I now know more about this than any of the practitioners who are going to get these calls and I have no clue what to do. I mean I have no idea whether it would be better to continue the medicine and maybe it's going to help or better to stop it. That's my problem is if you interpret to the healthcare provider we're kind of -- I mean we're not being that helpful to them.

DR. WARD: But doesn't that support Melissa's compromise? I think that's very appropriate and consistent with what we know and don't know.

DR. HAVENS: That's only going to be helpful if there is a discussion about some -- Then you have to make the discussion a little longer to bring people up to speed about what we know. Some people continued the drug and didn't have another event. Some people seem to get recurrence of the same event with each time they took the dose. So that's we don't

know what to do because it's different in different people. But this -- it to the local -- To me, that's bad. I agree. You can't do that.

CHAIRPERSON RAPPLEY: Dr. Gorman and then Dr. Rosenthal.

DR. GORMAN: I think that when we start to prescribe individual practitioners' courses of action we are practicing medicine and I'm not sure that's what the label should do. I think we present the information to the practitioners and the careful thoughtful processes or unthoughtful processes that they go through when they make decisions. But if you had information that said you should stop, then I think it should be there. But if we had information that said you should not stop it should be there. I don't think we have either of those pieces of information.

DR. HALL: If I can just add to that and just say that you already have in here the relative contribution of the drug of these

events is not known. Just leave it at that. Obviously, anybody can make their decision from there on rather than we should prescribe what they think since we have no information.

CHAIRPERSON RAPPLEY: Dr. Rosenthal.

DR. ROSENTHAL: I was just going to say that I've forgotten what the second question is that we're answering.

(Laughter.)

CHAIRPERSON RAPPLEY: We'll get to it really shortly. So this is the last thing regarding question one and that has to do with Melissa suggested a compromise. Are people generally in favor of that compromise language?

DR. WARD: Could I suggest either that or be silent?

CHAIRPERSON RAPPLEY: Have we been definitive enough for you?

DR. MURPHY: We have enough.

CHAIRPERSON RAPPLEY: Okay. So we can move onto question number two and question

number two based on the totality of data presented today on neuropsychiatric events and the possible relationship to zanamivir does the current labeling for zanamivir adequately address the safety concerns regarding neuropsychiatric events. Yes or no?

DR. MURPHY: I guess if I could clarify that a little bit, I guess we'd just like to know if you think these events are different between Tamiflu and zanamivir regardless of what we know or don't know about the CSF penetration of any of these products. From what we've heard today, what do you think the labeling should be?

CHAIRPERSON RAPPLEY: Dr. Havens.

DR. HAVENS: One of -- It seems like there may be a relationship, although less strong. There is less data because there are fewer patients treated. One approach that's been taken in other areas, for example, with NRTIs for the treatment of HIV is to look at some of these things as a class effect and

have sort of a general paragraph about lactic acidosis and hepatic ketosis or whatever.

We'd have a similar kind of paragraph here about influenza is bad for you and you have to worry about neuropsychiatric events and with the potential for some drug disease interaction that we don't really know but may or may not occur. That would be less specific to zanamivir for which there really are fewer data that would support a strong statement, but would again give the practitioner -- or would raise the possibility that this is somehow a class effect that gets around a specific drug effect problem.

I think this is a little trickier.

CHAIRPERSON RAPPLEY: Dr. Kimberlin.

DR. KIMBERLIN: I think that the biologic plausibility for zanamivir is even harder for me to get my arms around given the very low systemic bioavailability and even presumably a high CNS penetration and I think that the key word there is "presumption." To

imply causation here with the data we've seen is a stretch. Now whether it should be -- If the wording agreed upon with the question number one deals more with influenza as a disease entity, that's one thing. But to somehow link it with zanamivir when we know that systemic concentrations of drug are so low I think is challenging.

CHAIRPERSON RAPPLEY: Dr. Ward.

DR. WARD: I would agree with exactly what he said. But I think that you should try to couple the two. That is the issues about neuropsychiatric behavioral events occurring during influenza and during influenza treated with antiviral medications is worth including in there but with the further qualification that bioavailability systemic exposure is very limited.

DR. HAVENS: I like that approach to the problem.

CHAIRPERSON RAPPLEY: Dr. Newman.

DR. NEWMAN: Yes, I'd agree with

that, too. Most of the phrasing should probably be the same. So the most of the effort that would go into this could just be done once. But I think adding that caveat would be good.

I just wanted to make sure. Did we all agree that there would be some statement about the rarity of these effects or about the frequency? I just wanted to make sure that was covered. Okay.

CHAIRPERSON RAPPLEY: So is anyone opposed to what Dr. Ward has suggested? Dr. Fant.

DR. FANT: Yes. Just a couple of comments. I want to get back to your comment earlier about the class effect. I'm not sure I'm swayed or reassured about zanamivir because of its systemic absorption because the uncertainty that we've been wrestling with today in terms of whether or not there is an effect with Tamiflu, we have no idea what the mechanism is and so it's hard for me to be

reassured about another drug because it's not systemically absorbed because that's presuming what we think the mechanism is, getting from A to Z.

And so I'm not sure what the CNS levels are personally. I haven't seen anything that necessarily reassures me of that. I've seen some data to suggest that it's not likely to be high in most cases. Two, I don't know how high is high enough or how high it has to be in order to see an idiosyncratic reaction if that's in fact what's happening. Again, we don't know. So it's just hard for me to sort of separate the two.

And getting back to the point that you made earlier in terms of dealing with it as a class effect and not necessarily separating one medication from another, I think we sort of did this a few years ago with the antidepressants when we looked at the SSRIs and some of the other drugs that we

really didn't have enough information to limit our concern to one particular class of drugs and I'm not sure we know enough, we have enough information, to necessarily separate the labels or make them significantly different at this point.

CHAIRPERSON RAPPLEY: So we have two suggestions then, I think, out. One is to use essentially the same kind of information in a more generic way with zanamivir and the second is to add something additional that there is actually less reason to suspect adverse events.

DR. MURPHY: It might be good to do a hand raising.

CHAIRPERSON RAPPLEY: Okay. How many people would like to use the same general language for zanamivir as was used for oseltamivir?

(Show of hands.)

CHAIRPERSON RAPPLEY: I count 11. Is that what you counted? I see need the hands

up. Put your hands back up again.

(Off the record comments.)

CHAIRPERSON RAPPLEY: Okay. Those opposed?

(Show of hands.)

CHAIRPERSON RAPPLEY: Opposed to using the same label, the same generic information.

DR. WARD: Yes, without any qualification about its lower bioavailability.

CHAIRPERSON RAPPLEY: Yes. Do we have to take an opposed and then an abstention on every vote?

DR. HAVENS: I would. The same general information would be the same general information but that from my perspective would include the issue of the caveats about a lower bioavailability potentially.

CHAIRPERSON RAPPLEY: No. That's what I separated. So the first vote is to use essentially the same generic information. Let's see who supports that and your other

option is to support using the generic information plus a caveat about less evidence to suspect adverse effect.

Yes?

DR. ROSENTHAL: I'm not clear about the alternative. We're going to refer people to label of Tamiflu and say "We think it's even less."

CHAIRPERSON RAPPLEY: No. You don't refer people to another label, but it's just that they would repeat the same information. I didn't get the rest of your question.

DR. ROSENTHAL: What's the alternative if we don't use the same general label?

CHAIRPERSON RAPPLEY: The suggestion has been that we add language that we in fact expect fewer adverse events or less adverse outcome because of its bioavailability, something along those lines.

DR. ROSENTHAL: And that's my point. Fewer or less than what?

CHAIRPERSON RAPPLEY: Yes. That would be -- Yes, you're right.

DR. MURPHY: It doesn't work.

DR. HAVENS: Yes. You'd have to be very careful how you did that, wouldn't you?

CHAIRPERSON RAPPLEY: Yes.

DR. DAUM: To say we expect fewer events implies that we know what's happening.

(Laughter.)

DR. DAUM: Why it's happening and what to look for to say if it's happening more or if it's happening less, none of which I think we know.

CHAIRPERSON RAPPLEY: Okay. Would anybody support that kind of language then at this point in time?

DR. KIMBERLIN: I think that I would, if we're going to make a statement that goes beyond an influenza effect and move into a statement of an antiviral side effect or adverse event, then I think it warrants mention that systemic bioavailability is very,

very low with this drug.

DR. MURPHY: Okay. We got it. I think that there's an agreement that there's a general statement and that if we want to go beyond that general statement that for this product we need to make sure that we consider, we discuss adding something about bioavailability. In other words, if we're going to say that the contribution is unknown as you say it's going to be very tricky without making it any worse. I mean that's what you have to be careful that you don't do.

CHAIRPERSON RAPPLEY: Okay. So you're suggesting to consider --

DR. MURPHY: Yes, we will take into consideration that a number of member of the Committee were considered that if we're going to have the language that impugns antivirals that we have something about the difference of bioavailability of this product in that. It would be in addition to any general statement.

CHAIRPERSON RAPPLEY: And with that,

I'd like to move on unless these are really compelling comments because we have three more questions. They're dying over here. Okay. Dr. Gorman.

DR. GORMAN: I have a terrible sense of deja vu with Adderall and Ritalin where we're maybe driving the use of these drugs from one agent where we don't much about it, we're confused, to another agent where we know not much about it and we're confused in a sense if we put an escape clause for one of these agents in there we have the potential to drive use to an agent that we know less about.

CHAIRPERSON RAPPLEY: Yes, Dr. Fant.

DR. FANT: And I would just like to reaffirm my concern about making a point of the bioavailability of one drug because we have no idea if that's at all relevant to any role if any that it may have. And so its potential for being reassuring is in my view nonexistent. Assuming there is a role for these antivirals in the events that we're

seeing, it may be a secondary effect of killing the virus, some immunological reaction to killing the virus irrespective of where it happens and it doesn't really matter how much of it gets absorbed.

So I think to make a suggestion about putting that in there, I think, is probably more premature than drawing causality based on the information we have at this point.

CHAIRPERSON RAPPLEY: I think those last two points were well taken and you've taken note.

DR. MURPHY: Yes. And it is an issue that we would deal with and you're right. That would be one of the things that we would have to address that we don't put something in one product that would drive people to another product when you have equal unknownness here.

CHAIRPERSON RAPPLEY: Okay. We move onto question three. Based on the totality of the data presented today on neuropsychiatric events and the possible relationship to the M2

inhibitors, amantadine and rimantadine, does the current labeling for amantadine and rimantadine adequately address the safety concerns regarding neuropsychiatric events? Yes or no? Open for discussion. I hear a yes.

DR. NEWMAN: We haven't heard any data that would make us change those labels I don't think.

(Laughter.)

CHAIRPERSON RAPPLEY: So the suggestion is that we keep those labels the same. We don't offer suggestions to change.

DR. MURPHY: Okay. So what we're hearing is that no one has raised their hand to object and it's the unanimous opinion to not change those labels at this point.

CHAIRPERSON RAPPLEY: Is that correct? Okay. Yes, Dr. Rosenthal.

DR. ROSENTHAL: But I am not sure whether it would make sense if we're going to include a generic paragraph for agents that

are being used to treat influenza, I'm not sure that it makes sense to leave that out of the labels of other agents that are being used to treat influenza. I'll just throw that out, not that we need to discuss it.

DR. MURPHY: Is there a concern that we would drive patients to these products?

PARTICIPANT: Yes.

DR. DAUM: I have that concern.

DR. HAVENS: Yes. I think that's an important issue and it sort of freezes up the practitioner who has been told not to use them. So you have a bit little careful. You raise a very good point. If we're going to talk about influenza and potential neuropsychiatric complications, but only the newer product labels, then people might want to use an older -- or are reading that and might think "Oh, I'd better not do this" might go to other products as the points were made there before.

CHAIRPERSON RAPPLEY: And it does

punish people who do what they ask us to do which is bring us more information and rewards those who don't bring us information and we want to make sure we don't do that.

DR. MURPHY: Okay. So I have on the record that I just said we had an unanimous vote not to change these labels, but I guess I have to take that statement back now. Is that correct?

CHAIRPERSON RAPPLEY: I think Dr. Rosenthal made a good point.

DR. MURPHY: We have concern that as we do changes to the other products that we make sure that if there are general influenza concerns that they're in all the labels and as noted one of these labels already has a lot of CNS information in it. Okay.

CHAIRPERSON RAPPLEY: Question four. Do you have any suggestions for other studies or analyses that are feasible and might clarify this safety issue? Please comment. Dr. Ward.

DR. WARD: I would really like to see a case control type of a study of the neuropsychiatric events. I think we have to be looking at genotyping of individuals. I think we have to look at what their concentrations are. Is there something different about their clearance? I just think we need to continue in-depth evaluation of these events to try to understand why they're occurring and maybe it's as Dr. Okabe presented that it's a cytokine release that is excessive that would be consistent with a serious type of illness. But I just think we need to remain vigilant. That will improve our therapeutics.

CHAIRPERSON RAPPLEY: Dr. Kocis and then Dr. Kimberlin.

DR. KOCIS: I'm going to be brief here because I think this is going to extend to all the discussions over the next days and I'm sure in future years. But I was taken aback at we are the Pediatric Advisory

Committee and yet we can't define what a pediatric patient is. I've been reading all these studies all day long and we have kids who are 13 who are adults, 16 who are kids, 21 who are children and I think we need at the beginning to have data that's consistent to begin to understand and make sure there's no changing the numerators or denominators by looking at pediatric patients however we want to define that and just a segue we have a three month old neonates. So I think it's a bigger topic, but I want to bring that up.

CHAIRPERSON RAPPLEY: I think that's very consistent with our conversation in October from the cough and cold discussion about moving towards more standardized ways of obtaining data, analyzing or at least segmenting data and treatments. Dr. Kimberlin?

DR. KIMBERLIN: Earlier in the day, Dr. Havens mentioned natural history studies of influenza, so not just focusing on people getting a drug and what their particular

concentrations of genetic predisposition may be or whatever. But let's learn more about influenza as a whole. This is obviously a virus that causes tremendous disease burden and has been until perhaps quite recently very underappreciated.

CHAIRPERSON RAPPLEY: Dr. Gorman and then Dr. Daum.

DR. GORMAN: As I tried to say so clumsily in my discussion with the pharmaceutical representatives, I think retrospective collection of data in this is going to be very unproductive and a use of wasted resources. I would suggest that the pharmaceutical industry look at the Pediatric Research and Office Settings Network. It's approximately 5,000 pediatric offices in the United States where they would prospectively look at patients treated or not treated as long as they have the diagnosis of influenza by whatever diagnostic criteria you wish to use. But I think an antigen test would be a

minimum and then they can query those patients in 24 hours and 48 hours for neuropsychiatric events. These events are so fleeting and if there are a lot more of hallucinations with influenza without treatment, I would like to know about that as much as I would like to know about the neuropsychiatric events with treatment.

DR. WARD: Just to clarify. The PROS Network has been organized through the American Academy of Pediatrics that he's referring to.

DR. KOCIS: Thank you for that paid political announcement.

CHAIRPERSON RAPPLEY: Dr. Daum.

DR. DAUM: I would like to just follow up on something we started talking about briefly before and that is the idea of studying these drugs in a prophylaxis setting to see how they perform in patients who don't have influenza to try to tease out some of the effects. We got some reaction that it can't

be done and it's not feasible, but I think there are ways to do it. Taking the study to our Japanese colleagues might be one way to start getting some preliminary data. Doing it in the network like we just heard about might be another and it would be very interesting to see what data can be generated from that. I don't want to sit here and design the study in committee. I think that's probably going to be an all evening exercise. But I think some kind of data like that would be very, very helpful.

CHAIRPERSON RAPPLEY: Dr. Havens, did you have a comment?

DR. HAVENS: Well, just that I do think that we heard that there is a Roche-Kaiser Permanente study planned for this year and that I'm very supportive of having them make sure that their definitions match the FDA neuropsychiatric definitions. It seems like they did and I think that that would be a very useful first place to start and it looks like

it's ongoing.

CHAIRPERSON RAPPLEY: Dr. Rosenthal.

DR. ROSENTHAL: I share my colleagues' enthusiasm about studying prophylactic use of these medications and I just want to make a plug for maybe a little more scientific rigor in the assessment of the outcome perhaps by doing some neuropsychological testing on kids who are receiving these medications for prophylaxis. I mean it's one thing to have a child come running into their parents' room complaining that there's a six foot tall rabbit in their closet. But there may be other information that will help us to understand whether there are more subtle neuropsych effects of these drugs or from influenza.

CHAIRPERSON RAPPLEY: Dr. Cnaan.

DR. CNAAN: If studies are suggested, then I would like to make one design plug. The question we're answering is is the drug doing any harm and the numbers that were

posted up there for sample size are replicated in my own program. They are large. No question. If we want answers to these questions, we have to ask the question of "is the drug doing no worse?" Because if all we're going to ask is is there any difference and we design it even with 20,000 patients, we won't difference at the incidence rates that we think are underlying this thing. So non inferiority is my personal suggestion.

CHAIRPERSON RAPPLEY: Okay. Are those enough ideas for you to work with?

DR. MURPHY: Yes, it's very helpful. Thank you.

CHAIRPERSON RAPPLEY: So the last question is that presently the agency meets on a monthly basis during influenza season to review adverse events reports for the four influenza products. We plan to continue this current monitoring schedule. At this time, an update for future pediatric advisory committees is not planned. However, if

important safety concerns emerge, we will report back to the Committee. Does the Committee agree with this plan? Is anyone opposed to this plan? The Committee agrees.

Well, thank you all very much. It's been a very interesting day and thank you for your attention and staying with us to this late hour.

DR. MURPHY: Yes. We sincerely thank everybody for reading all the material, for a really good discussion and for the variety of comments. It's very helpful.

DR. DAUM: You notice we did not ask for a lot more material and questions this time.

DR. MURPHY: Caught you, didn't we?

DR. PENA: If people can leave their meeting materials at the desk for day one, we can take them off your hands and shred them.

CHAIRPERSON RAPPLEY: Off the record.

(Whereupon, at 5:27 p.m., the above-entitled matter was concluded.)