UNITED STATES OF AMERICA

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

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CENTER FOR BIOLOGICS EDUCATION AND RESEARCH

VACCINES AND RELATED PRODUCTS ADVISORY COMMITTEE

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MEETING

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FRIDAY, NOVEMBER 20, 1998

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The Committee met in Versailles Rooms I and II, Holiday Inn, Bethesda, Maryland, at 8:00 a.m., Patricia L. Ferrieri, M.D., Chair, presiding.

PRESENT:

PATRICIA L. FERRIERI, M.D., Chair
NANCY CHERRY, Executive Secretary
REBECCA E. COLE, Member
ROBERT S. DAUM, M.D., Member
KATHRYN M. EDWARDS, M.D., Member
DIANNE M. FINKELSTEIN, PhD, Member
HARRY B. GREENBERG, M.D., Member
CAROLINE B. HALL, M.D., Member
ALICE S. HUANG, PhD, Member
KWANG SIK KIM, M.D., Member
STEVE KOHL, M.D., Member
GREGORY A. POLAND, M.D., Member
DIXIE E. SNIDER, JR., M.D., MPH, Member

OPEN

PRESENT: (continued)

Invited Participants:

ROBERT BREIMAN, M.D.
ROBERT CHANOCK, M.D.
NANCY COX, PhD
THEODORE EICKHOFF, M.D.
EDWIN KILBOURNE, M.D.
BRIAN MURPHY, M.D.
GEOFFREY SCHILD, PhD
ROBERT WEBSTER, PhD
PETER WRIGHT, M.D.

DR. ROLAND LEVANDOWSKI, Speaker

I-N-D-E-X

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

(8:02 a.m.)

CHAIRPERSON FERRIERI: Good morning, everyone. Good morning. I'd like to call the meeting to order, if you could all takes seats, please. I'm not in fine singing form this morning to sing "You Are My Sunshine," but the equivalent of that plea is in our thoughts as we resume our seating here.

Members who have been designated by Mrs. Cherry, please take your seats, and then the audience. Good morning. I'm Patricia Ferrieri, the Chair of the Vaccines and Related Biological Products Advisory Committee. We are in open session this morning, and I'd like to start by making introductions.

It looks like some of our members aren't here, but you will see them joining us shortly, I hope. I'm from the University of Minnesota Medical School. I'd like to start at Dr. Greenberg's end at my far right, if you could give your name and institutions, please.

DR. GREENBERG: Dr. Harry Greenberg, Stanford University and the Palo Alto V.A. Hospital.

DR. EDWARDS: Kathy Edwards, Vanderbilt University, Nashville, Tennessee.

DR. SNIDER: Dixie Snider, Centers for

Disease Control and Prevention.

DR. KIM: Kwang Sik Kim, Children's Hospital Los Angeles.

DR. HALL: Caroline Hall, University of Rochester, Rochester, New York.

DR. KOHL: Steve Kohl, University of California San Francisco.

DR. HUANG: Alice Huang from Cal Tech.

MS. COLE: Rebecca Cole, Consumer Representative from Chapel Hill, North Carolina.

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

MS. CHERRY: Nancy Cherry, FDA.

DR. EICKHOFF: Ted Eickhoff, University of Colorado, Denver.

DR. SCHILD: Geoffrey Schild, NIBSC, United Kingdom.

DR. CHANOCK: Robert Chanock Allergy/Infectious Diseases Institute, NIH.

DR. MURPHY: Brian Murphy, the same.

DR. WRIGHT: Peter Wright, Vanderbilt.

DR. COX: Nancy Cox, CDC.

DR. WEBSTER: Rob Wester, St. Jude Children's Research Hospital.

CHAIRPERSON FERRIERI: Thank you. As we

continue during the morning, I would like to advise everyone that FDA has set this schedule and the timing -- the timeline here, and committee members are taking this very seriously and have planes to catch.

So we will adjourn at one o'clock, whether we are through or not. Those of you who watched the hearing yesterday know how very gracious Henry Hyde can be, but I haven't taken lessons from him, but occasionally I'll refer to Dr. Edwards as my distinguished and gentle colleague from Tennessee.

Well, we'll start with the open public hearing. I'll turn this over to Mrs. Cherry.

MS. CHERRY: At this time, this is an opportunity, if there is anyone in the audience that wishes to come forward and make a statement.

If there is no one, then we will proceed with the meeting.

CHAIRPERSON FERRIERI: Thank you. The session is on live attenuated influenza virus vaccines, a rather general session, and the introduction and objectives will be presented by Dr. Roland Levandowski from FDA. Good morning, Roland.

DR. LEVANDOWSKI: Good morning. Thank you, Dr. Ferrieri. If you can't hear me, I'm told that I'm sometimes not close enough to the microphone.

So if I'm fading out, would you give me a push and remind me to get up here, because I do want people to hear what I've got to say. Could somebody turn on the first slide, please, or can I do that from here? Thank you.

We're here this morning to talk about live attenuated influenza virus vaccines. Clinical trials completed during the current inter-pandemic period have demonstrated the feasibility of producing live influenza vaccines for the prevention of naturally occurring influenza.

In the future, product license applications for live influenza vaccines may be brought before the Committee for specific advice. However, today we are asking the Committee to consider and discuss in a very general sense some aspects with known or theoretical capability to affect the safety of life influenza vaccines.

The large scale of live influenza vaccines in the United States, particularly in pediatric practice, has already been discussed at other earlier meetings of public health and medical organizations. The potential exposure of a large segment of the population to a potentially transmissible and infectious agent prompts us to raise issues of generic

interest to the individual and society.

Some of the issues for discussion this morning have been raised previously by members of the medical and pharmaceutical communities involved in the exploratory work. However, it seems appropriate to revisit some topics, particularly where additional information has accumulated and understanding is more profound.

In order to focus the discussion, I will first list the issues, and I will then briefly present some background information. The speakers who come after me this morning will address specific topics in greater depth.

This slide shows the issues for discussion. By the way, the Committee has in front of them a packet that should have these slides, so that if you're having trouble seeing the screen from where you are, you can refer to the information packet.

This slide shows the issues for discussion. We ask that the Committee first comment on markers used to predict the attenuation of life attenuated influenza virus vaccines.

It is now possible to understand attenuation at the molecular level. However, life influenza vaccines will undoubtedly face the regular

challenge of keeping up with antigenic changes, just as the inactivated vaccines do now.

If genetic composition has any unpredictable expressions, then what phenotypic markers would be needed to ensure the reliability of life influenza vaccines?

We also ask the Committee to comment on biological containment for the development and manufacture of live attenuated influenza virus vaccines. When new strains that appear with the potential to spread widely, what control measures will prevent the premature release of a strain of unknown pathologic potential?

Please keep in mind that manufacturing facilities are very specifically designed to protect products form contamination and not to protect the environment from the product.

The experience of reintroduction of the H1N1 influenza A viruses in man in 1977 perhaps illustrates the concern. Genetic analysis of the 1977 H1N1 strain shows very clearly that it is related to viruses from the 1950s and does not represent a strain that was undergoing continued evolution in nature.

The observation is so striking that this H1N1 virus has been described as being frozen in time,

with the implication being that it quite literally went from prolonged storage in a freezer into a population susceptible after 20 years' absence of the strain.

The non-trivial nature of the event is demonstrated by the fact that H1N1 influenza A viruses have continued to circulate, have produced epidemics, and have undergone substantial natural antigenic evolution during intervening years.

We also ask the Committee to comment on the introduction of new influenza virus strains, and I'll emphasize strains, and subtypes into the community in the form of live attenuated influenza virus vaccines.

For example, if introduction of a new strain is purposeful, what is the probability that a natural reassorting event would produce a nonattenuated strain? If the situation arises that a strain with potential to spread widely is identified but remains confined to a small geographic region, what safety concerns should be entertained in conducting clinical trials?

A similar situation has already been encountered with the H5N1 viruses in Hong Kong, which caused infections in man but failed to spread to other

areas of the world.

Finally, we ask the Committee to comment broadly on possible clinical consequences of live attenuated influenza virus vaccines, including secondary bacterial infections and hypersensitivity reactions.

What information should be gathered or what studies should be performed to understand the incidence of adverse experiences that might logically be expected to occur with influenza viruses grown in eggs?

I'll begin by reviewing some general features of influenza viruses and vaccines. Influenza A and B viruses produce the febrile respiratory illness that we call influenza or grippe, and during the winter months of most years influenza A and B viruses produce epidemics in the United States that are characterized by serious morbidity and mortality.

Unlike influenza B viruses, the influenza A viruses can be divided into a large number of antigenically distinguishable subtypes based on characterization of the hemagglutinins and neuraminidases of the viruses.

Although influenza B is almost entirely confined to human populations, influenza A viruses

infect many animal species, and birds in particular serve as the natural reservoir for preservation of the 15 known hemagglutinin subtypes and nine known neuraminidase subtypes.

Currently, two subtypes of influenza A are present in human populations, the H3N2 viruses that first appeared in 1968 and H1N1 viruses that reappeared in 1977 after a 20 year absence. H2N2 viruses have also circulated widely in human populations, but were last found during the years between 1957 and 1968.

More recently, the H5N1 influenza A viruses in Hong Kong during 1997 demonstrate definitively that additional subtypes of avian origin can infect man and cause serious respiratory illness and death.

This figure is the cartoon structure of an influenza virus, and it shows the eight gene segments of the virus and the structural proteins of the nucleocapsid and lipid envelope. The genetic complement of an influenza virus determines the host range of the virus and appears to be optimized for specific hosts. Thus, human influenza viruses appear to be optimized for persistence in man, and animal strains appear to be optimized for their animal hosts.

The segmented nature of the influenza virus genome also has distinct implications for the ability of influenza viruses to persist in the environment. In particular, mixed infections permit shuffling of gene segments to produce new combinations that may alter the phenotypic characteristics. It's what we refer to as reassortment.

This slide shows -- I don't know if that's in focus; it's kind of fuzzy to me. So maybe someone could see if they could focus that. This slide shows the full gene complement, polymerases, PB1, PB2 and PA, hemagglutinin, nucleoprotein, neuraminidase, matrix and NS of the H1N1, H2N2, and H3N2 viruses in man during the 20th Century using the H1N1 strain as the root.

At least twice, in 1957 and again in 1968, reassorting events involving human and avian influenza A viruses resulted in pandemics of influenza with rapid dissemination of the new reassortant viruses. In both events, new avian influenza virus genes were introduced into human influenza virus strains.

It is possible that the transfer of the hemagglutinin gene alone was sufficient to establish the new reassortant viruses in man, but the fact that one of the polymerase genes was also exchanged on each

occasion suggests that other properties affecting the host/parasite interaction could be transferred independently.

As has been determined, for the recent Hong Kong H5N1 influenza A viruses, a full complement of avian origin genes in the absence of -- where there was a full complement of avian genes in the absence of reassortment with a human influenza A virus, that may very likely explain the failure of the H5N1 viruses to spread in man.

Now reassorting, however, also offers advantages in controlling influenza viruses. Influenza viruses are readily reassorted in the laboratory, and it is frequently possible to select progeny viruses with attributes from a wild type influenza strain and a donor with specific desirable properties.

For example, reassortant viruses capable of high growth in eggs and having the hemagglutinins and neuraminidases of new wild type strains have become increasingly important to permit production of inactivated vaccines to keep up with increasing demand.

Likewise, the ability to produce reassortants between wild type strains and strains of

greatly reduced virulence has permitted the development of live attenuated influenza virus vaccines.

The next series of slides describe the clinical features of naturally occurring influenza virus infections in man. Influenza viruses are spread among people both by infected aerosols and by direct contact with the infected secretions of other persons or animals.

The infectious dose is variable, and it relates partly to the previous immunologic experience of the host and partly to the number of infectious units in the inoculum. The viruses replicate predominantly in the respiratory epithelium, but they may also be found in monocytes, macrophages and polymorphonuclear leukocytes.

The illness produced by influenza viruses consists of a well described constellation of local respiratory and systemic symptoms, and these symptoms, of course, include sore throat, sneezing, nasal obstruction, nasal discharge, cough, fever, malaise, myalgias and headaches.

The pathophysiology underlying these symptoms relates to the replication of the viruses and the host responses to them. For example, influenza

virus infection is associated with release of a number of inflammation inducing and augmenting mediators, including interleukin-1 and TNF alpha.

It has been well documented that bacterial pneumonia is more frequent following an acute episode of influenza virus infection, and the bacteria found as the cause routinely include hemophilus influenzae, staphylococcus aureus and streptococcus pneumoniae.

In addition, infections of the paranasal sinuses and the middle ear are also increased in frequency following influenza virus infections, and may be associated with the same types of bacteria.

The association of bacterial infection with influenza may be a result of the effects of influenza viruses on host defenses. Very prominently, even in uncomplicated influenza virus infections, respiratory tract clearance mechanisms are disrupted by damage to the ciliated respiratory epithelial cells.

Chemotaxis, phagocytosis, bacterial killing and other functions of leukocytes are impaired by influenza virus infection, and alterations in the cell surface also occurs, as shown by the enhanced ability of bacteria to adhere to infected cells and to grow in the respiratory tract.

Other less common complications include primary influenza virus pneumonia that may occur with or without concurrent bacterial pneumonia. The development of viral pneumonia reflects the ability of influenza viruses to replicate at temperatures of 37 Centigrade and above in the trachea, branchiae and alveoli.

Disorders outside the respiratory tract during and following acute influenza virus infections have been reported anecdotally very infrequently; but extrapulmonary disorders have been linked to influenza virus infections on the basis of serological evidence of a recent influenza virus infection or recovery of a virus from the respiratory tract.

Myositis, myocarditis and pericarditis have been associated in a few instances with the recovery of an influenza virus from the affected tissues, and a variety of neurological syndromes, including Reyes syndrome, encephalomyelitis, meningitis and Guillain-Barre syndrome, have been reported following an acute episode of influenza, but in the vast majority of patients no influenza virus has been recovered from neural tissue.

Death is noted here as a rare complication of influenza, which it is as a percent of all

influenza virus infections. However, since influenza is such a widespread illness, the absolute toll of tens of thousands of excess deaths during influenza epidemics is actually quite substantial.

All of these examples of what influenza viruses can do in man, of course, are exactly what live vaccines should not do if they are to be valuable.

The primary means of controlling influenza for more than 50 years has been inactivated influenza virus vaccines. The inactivated vaccines work mainly by producing systemic IgG type antibodies to the hemagglutinins of influenza viruses. Mucosal secretory IgA type antibodies are not as reliably induced, and little or no evidence for cytotoxic T-cells can be demonstrated in response to an inactivated influenza virus vaccine.

Although systemic antibodies do not necessarily prevent subsequent infection, inactivated vaccines have repeatedly demonstrated efficacy in reducing the incidence of complications, including pneumonia and otitis.

Live influenza vaccines have received attention, because they more nearly mimic natural infections by replication in the respiratory

epithelium of the host, and they induce a wider array of immunologic responses, including local mucosal antibodies and cytotoxic T-cells.

Because of this potentially broader immune response, it has been hoped that live influenza vaccines may offer advantages in protective efficacy. The search for attenuated influenza viruses for use in vaccines has extended over more than 30 years. This table lists only a few of the viruses that have been explored for use as donor strains for vaccines studied in clinical trials.

A/Puerto Rico/8/34, which is known to many simply as PR8, and A/olcuda/57 are primary examples of strains that were passed multiple times at typical permissive temperature of 33 Centigrade to result in attenuation of the donor strain for man.

In the case of both the PR8 and the A/olcuda donor strains, attenuation of reassortants was somewhat unpredictable, and viruses clinically more virulent than the original wild type strain were occasionally produced. However, techniques to precisely define the genetic composition of the resulting reassortants were not available at the time of the clinical studies, and it may be that failures of attenuation were related to retention of wild type

virus genes conferring virulence.

The passage history for the so called cold adapted strains is better recorded. Detailed information exists on the strains of origin and on the passage histories to produce the attenuated master viruses used for reassorting.

These strains are called cold adapted, because they have undergone multiple passages at increasingly lower temperature to yield viruses that are characterized by the ability to replicate at 25 Centigrade but not at 39 Centigrade.

A multitude of influenza A and influenza B virus cold adapted reassortants have been tested in clinical trials, and the data to date suggests that the cold adapted strains are well attenuated and unlikely to revert to virulence by way of spontaneous mutation.

In the case of the A/Leningrad virus, master strains at two passage levels have been used for different purposes. One master strain passage 17 times before reassorting appeared to produce clinical symptoms suggestive of influenza in a relatively high proportion of children. However, an additional 30 passages of the A/Leningrad virus resulted in a strain with much greater attenuation for use in children.

The experience, I think, emphasizes that the passage history of the donor strain significantly controls the attenuation phenotype.

The last column of the table gives a rough indication of the number of persons who have received one of the live influenza vaccines made with attenuated donor viruses. While very few people have received the PR8 or A/okuda reassortants, the experience with cold adapted strains such as the Ann Arbor and the Leningrad strains is quite broad in terms of special risk groups and age groups receiving vaccine and, in particular, children.

The most extensive clinical experience with live attenuated viruses is in the former Soviet Union and Russia where some number of millions have received live influenza vaccines. Some information on the experience there has been published in recent years, and has been generally favorable on the safety and efficacy of the live vaccines; but more detailed data would be useful for assessment of rare types of adverse events.

The need for replication of live influenza vaccines in the host requires a degree of host susceptibility to infection. It also implies the theoretical possibility that coinfection by a wild

type virus and a vaccine virus could result in viruses with the virulence of the wild type, but the hemagglutinin and neuraminidase of the vaccine virus.

Examples to prove the feasibility of reassorting in man include multiple demonstrations of H3N1 and H1N2 viruses. However, the fitness of the H3N1 and the H1N2 viruses may be limited, since they do not appear to have persisted for very long when identified.

In the same vein, a reassortant virus of a new influenza A subtype, even if attenuated, raises the possibility of introduction of that new subtype, particularly if the immunological experience of the population as a whole is important to limiting transmission of vaccine viruses. As noted earlier, the return and persistence of H1N1 influenza viruses was made possible partly by the development of a large 20-year cohort of susceptible people.

As a final comment related to vaccines, whether or inactivated or live, all current vaccines are produced in the allantoic fluids of chickens' eggs -- that is, the egg white. While purification processes have been devised to remove egg proteins and lipids, even minute residual amounts of contaminating egg proteins appear to be sufficient to cause

reactions -- cause the rare anaphylactic and anaphylactoid type reactions in sensitized individuals who receive an injection of inactivated vaccines.

It has been very clearly shown that inhalation of egg proteins can be sensitizing with sufficient exposure. Although the dose response relation for sensitization is currently not defined for live influenza vaccines, the experience from clinical trials with vaccines produced as infected egg allantoic fluid harvests suggests that sensitization and hypersensitivity responses may be very rare. However, since live influenza vaccines are administered by way of the airways and are likely to be repeatedly administered, sensitization would seem to be at least theoretically plausible, as it could be for any vaccine produced in eggs.

This concludes my remarks, and the speakers who follow are going to elaborate on some of the other more specific details.

CHAIRPERSON FERRIERI: Thank you very much, Roland.

The next speaker is Dr. Brian Murphy from the NIH, and he will speak on pre-clinical studies with live attenuated vaccines.

DR. MURPHY: I wanted to thank Peter

Reeves for asking me to come and speak today. A lot of the data I'm presenting was actually done by Mary Lou Clements, who we had a few moments of silence for yesterday, and I'm proud to be able to present some of this to you today for your consideration.

I don't want to repeat anything that Roland has said. He gave an excellent review of the virus. I just wanted to point out one thing, that immunity to influenza is conferred by antibodies to the hemagglutinin and the neuraminidase.

This is very important. These genes must come from new variants as nature deals them to us. Okay. The way the influenza virus eludes antibodies' immunity induced by prior infections is a result of antigenic shift and antigenic drift.

Antigenic shift is simply the acquisition of point mutations within the HA and the NA glycoproteins, and this is antigenic shift. Excuse me. This is right. You acquire a new hemagglutinin neuraminidase.

Drift is where you accumulate point mutations in the epitopes of protective antigens. This occurs continually. These viruses appear, become the predominant strains. This occurs, and Roland indicated in our -- in the human population it

occurred in '57, '68, and then we had the unusual reoccurrence of the h1N1 virus and reappearance of it in 1977.

That's all the history of influenza viruses I'm going to talk about today.

Now the rest of the talk I'm going to be talking about the cold adapted A/Ann Arbor virus developed by Dr. John Massab. This is a result of an extensive series of studies that have been done by the intramural and extramural branch of NIAID and various vaccine evaluation units throughout the United States.

Although I'm predominantly talking about this particular donor virus, the point that I'm going to make, I think, for the Committee's perspective, can be thought of as a way to evaluate any particular candidate live attenuated virus that might come before the Committee. Okay?

So the general scheme of developing a live attenuated virus vaccine is to take a donor virus, mate it with a wild type virus. In this case, we're talking about an H3N2 wild type virus, and this is a virus that can be either an antigenic drift strain or an antigenic shift strain.

You mate it, and then you isolate reassortant viruses that contain the hemagglutinin and

neuraminidase of the wild type virus, because you want to develop antibodies that will protect you. These are systemic and mucosal antibodies that will protect you against this particular virus infection.

The attenuating mutations should be present on these other genes. Okay? This can be done for any virus, H1N1, and I'm going to be describing a series of H3N2 and H1N1 reassortants that have been generated over a period of about 15 years, and we will look at some of their properties.

Now the first question that was asked -- I have actually an earlier form of the questions before they were -- I had five questions rather than four, and my slides reflect that, but they're very similar to the questions that Roland -- these are like the first draft or the second or third draft. Roland gave you the fourth draft.

Are there adequate markers to predict the attenuation of cold adapted vaccines for use during periods of antigenic shift -- drift here. The answer to that is absolutely yes. Okay?

These are the markers that are associated with this particular virus. It's a temperature sensitive virus. It's cold adapted, which means it replicates efficiently at 25 degrees, in contrast to

wild type virus.

Now the other marker is that, if it has this particular gene constellation, two genes from the new wild type virus, six genes from the donor virus, this is a marker of attenuation. These have all been attenuated in rodents and ferrets, if they have this set of markers.

I think we can really basically consider this set of markers. Now will this predictably -- If a virus contains this set of markers, will this predictably attenuate a virus for humans? This is the first series of questions I'm going to be addressing.

Now to understand the genetic base of attenuation of this virus, extensive studies were done to evaluate the genes that are associated with attenuation. I'm going to give you a two-minute or one-minute review of this.

Take the cold adapted virus. Take wild type virus and then you take the cold adapted donor virus in this case. Actually, this is a reassortant that contains the same hemagglutinin and neuraminidase.

You mate these, and you devolve single gene reassortants, one gene from the cold adapted virus, all the others from the wild type, and you look

at this. This particular virus was looked at in ferrets, in hamsters and humans.

From an analysis, an extensive analysis, of this and from an extensive analysis of the sequence analysis done by Nancy Cox and her colleagues, the following three genes were associated as single genes as contributors to the attenuation of this virus.

Two genes confer the ts phenotype. These are the PB2 gene and the PB1 gene. The PA gene confers the cold adapted phenotype. Each of these genes are independent attenuating mutations.

We did not evaluate -- and this was a deficiency of our study. We did not evaluate various combinations of other genes, because this is too extensive an analysis. You can think of all the possible combinations of reassortant viruses you can generate. But it's very clear that you have at least three independent attenuating mutations, and the data was suggestive that there is an independent contribution by the NS and the M proteins as well -- the M genes as well.

There are -- There's a total of six mutations in these three genes that are associated with these genotypes, as far as we know.

Now what properties of an attenuated virus

do you need to evaluate in its reassortants? The reason influenza viruses are so complicated is you don't just approve a product. You have to approve a process, and the process is the passage of a set of six genes to a new wild type virus, and then evaluating the properties of those reassortants.

This has been extensively. Okay? These are the properties that we've looked at: Attenuation, infectivity, genetic stability, transmissibility and efficacy, efficacy in young children, adults and elderly. I won't go into these properties right now. I will show you the evidence that shows that the set of six genes and the markers are associated with the consistent transfer of these properties.

Infectivity: Infectivity is determined by doing dose response curves, different dilutions of the different quantities of virus and the cold adapted reassortant administered to humans, and the percent infected are determined.

You can determine a 50 percent infectious dose. Now are we able to reproducibly transfer a property of infectivity? The answer is absolutely yes. In adults, these adults generally are individuals or, obviously, are individuals who all had prior experience with influenza viruses. Pediatric

subjects represent immunologically naive subjects in this case.

In the adults, the property of infectivity for a variety of H1N1 and H3N2 viruses was very reproducibly attenuated. H3N2, H3N1 viruses, H3N2 very similar levels of infectivity, same for the pediatric titrations. I'm sure more of these exist out there now, but I think we can very comfortably say that the virus transfers the property of infectivity in a reproducible manner.

How about safety level, replication, genetic stability and transmissibility? This also has been reproducibly transferred. The safety -- In this case, we've just illustrated systemic illness here, in each case cold adapted reassortants. I don't know whether you can read it, but these are two H3N2 reassortants representing drift strains, and the same thing for the two H1N1 viruses.

This study right here actually represents a situation that mimics a pandemic situation in that the population lacked antibody to the H1N1 surface glycoproteins, but had prior experience with other related genes of the influenza virus.

Clearly, highly attenuated in humans, reproducibly so. Now here is the point, and Roland

raised the important question, is this virus going to cause secondary bacterial infections. Not only is it direct data that Peter Wright will talk about, but the reason it is not associated with significant secondary bacterial infections is because it's highly restricted in replication in the respiratory tract of humans.

I think we can see that wild type viruses generally grow about five logs. These viruses generally grow mean titers of around two logs. Okay? Also, the reason these viruses are poorly transmissible from human to human is because they grow so relatively inefficiently.

We're lucky, because although they're this restricted in replication, they're still able to induce a highly protective immune response, and I will demonstrate some of the data on that subsequently.

The level of replication is in part a function of the level of prior experiences humans have with the viruses. Wild type virus in adults will have a pattern of replication achieving titers of 10^5.

In seronegative individuals, absolutely naive, no experience with influenza viruses, a cold adapted virus will grow about at 10^3 and will have a replication maybe growing a little longer than the wild type virus. Seronegative adults' pattern looks

like this. The elderly actually have -- in our experience, have replicated the virus to the least extent.

Okay. Are these viruses genetically stable? I just want you to focus in on the upper part of this curve, a variety of H3N2, H1N1 viruses, six genes to the CA, no genes from the wild type except for the hemagglutinin and neuraminidase, various adult and pediatric populations, a large number of isolates tested. Much larger numbers have been tested other than this. This just illustrates it.

In every case the CA and the ts property of this virus was maintained. Now this is amazing that the ts property is stable as this. I've tested viruses that contained mutations on the PB2 and the PB1, ts mutants on the PB1, and the first volunteer that I gave it to we had revertants in both genes.

This virus we've given -- has been given to thousands of individuals, and we've not seen a revertant, as far as we could tell, on either of these two genes. I think it's because this is remarkable genetic stability and I'm surprised by it, but I think it's because there are nontemperature sensitive attenuation mutations that restrict the replication of this virus, making viruses that have lost the ts

phenotype less likely to emerge as predominant populations.

Okay. The property of genetic stability is reproducibly transferred. Same thing, lack of transmissibility has been studied, and this has also been shown to be -- the lack of transmissibility has also been shown to be reproducibly transferred to go along with the 6/2 gene constellation. This was done to two H1N1 viruses and H2N3 viruses. These are the number of infected vaccinees. These are their contacts, and it just simply does not spread.

The reason it doesn't spread is very simple. The monovirus that is generated in the respiratory tract of humans is around 10^3. The human infectious dose for adults is 10^5. In that context, this virus is not going to efficiently transfer. That doesn't mean it won't occur, but it's certainly not an efficient process.

Okay. Efficacy: I'm not going to go into a large amount of efficacy data. The important point I want to make here is that the property of efficacy has also been reproducibly transferred with the set of six genes. These studies that I've been talking about have all been done with monovalent vaccines.

This is the pre-clinical evaluation of

these cold adapted viruses, whereas the current studies are being done with trivalent vaccines. So we're talking about efficacy as it applies to monovalent vaccines.

I don't -- We don't really need to go too much into this, except this is studies that have been done in adult volunteers with challenge -- who were challenged. This is the percent reduction in virus shedding. I think you can see it's relatively high level of virus shedding and protection against systemic illness, a high level of protection, and in this case there were seven or eight different -- six different viruses that were tested, reproducibly transferring this property.

This is also true if you look at seropositive adults, adults not selected to have low HAI titers. You can protect individuals with these attenuated viruses, reproducibly, H1N1, H3N2 viruses in this setting.

Pediatric populations: What you do in a pediatric population -- you don't challenge them with wild type virus. You simply give them the second dose of the attenuated virus and, because it grows well in that population, you can quantitate the amount of virus that is secreted by the individuals.

In this case, there's a high level of reduction of virus shedding, again a reproducible transfer of this property. It's getting pretty boring, actually, isn't it? I mean, I recently studied this, and the last time I kept on saying why am I doing another one.

John Treanor did a very interesting study, and he was looking at how can these viruses be used in the elderly. Okay? Since the inactivated vaccine is licensed, he did a controlled trial where he gave some elderly the inactivated, and the inactivated plus live, and there were a number of subjects.

The efficacy scores in three separate circumstances, in three separate epidemics that were tested, were approximately 60 percent efficacy above that conferred by the inactivated vaccine alone.

Again, what I'm just pointing out here is the efficacy of this virus in this particular context also has been reproducibly transferred with this set of six genes.

Okay. These are the number of times safety has been looked at, infectivity, immunogenicity, these various other properties. You can look at it, number evaluated, number of times demonstrating the property, an extremely reproducible

set of findings.

I can say that I tried many vaccines. I mean, I have more failures than anybody I can imagine with this particular virus. This is the only virus that survived that had a pattern like this. We look at temperature sensitive viruses, host range, reassortants, a variety of other things. This is the vaccine's history right now.

I won't go into this right now. I think all these points have been made.

Now question 1(b): Are there adequate markers to predict the attenuation of the cold adapted live virus vaccines for use during periods of antigenic shift? The answer, I think, is yes. Okay?

This is certainly true for -- There's information that exists for H1 and H3. The H1, as I said, is a 1957 example, mimicked the pandemic, and all the studies that are done in young infants who are immunologically naive mimic a pandemic situation, i.e., individuals who have no prior experience with influenza viruses.

This has been tested multiple times. A lot of the data I presented previously had that information.

Okay. So that's what this is. Now is

there information for subtypes other than H1 and H3? The answer is no, and I think that one of the projects of NIAID, and we're initiating this now, is to develop experience with the cold adapted and activated vaccines bearing new and different hemagglutinin subtypes that could appear in the human population in the future.

Question 2: Comment on the level of attainment necessary for the development and manufacture of these vaccines.

Influenza A and B vaccines -- viruses are BL-2 viruses. There's really -- This virus has been given at 10^7 infectious units to 12,000 individuals to date. There really are no safety issues that you have that are related to the manufacture of this particular product.

In fact, it's analogous to the situation where -- like the vaccinia virus, which is a BL-2 virus, but the attenuated derivatives of vaccinia are basically -- now have been considered by the NIH safety committee to be having -- to be BL-1 agents. I would say there's enough experience to consider suggesting that these viruses could be similarly classified.

At the time of a pandemic -- okay? -- you

have a different situation. I think most people believe for influenza viruses, especially since what happened in 1997 where the H5 virus entered the human population and was associated with a high level of mortality, that people do not want to work with the hemagglutinins that have a highly cleavable phenotype, which is the phenotype that's associated with that mortality.

So I think that a major goal would be to work with viruses for both making inactivated vaccines as well as making live attenuated virus vaccines that have altered -- that have hemagglutinins that lack the phenotype of high cleavability. In that context, I think that we can work very safely with these viruses under the current practices of containment.

Now this is the major -- last question I'm going to be addressing. That is the -- Please comment on the risks associated with the use of live attenuated virus vaccines within the community. I'm giving you my opinion here, and I will show you why I've formulated this opinion.

I'm first going to be talking about the interpandemic situation, and this is what we have been in, an interpandemic situation, for the last 30 years. So this is the major situation that we really need --

this is a major situation, the predominant situation with influenza viruses in the human population.

What do we know about the epidemiology of influenza viruses that would help us in our analysis of the risks? These are the viruses -- This is the evolution of the virus. This is very similar to what Roland showed you earlier.

H1N1 viruses in 1934 appeared in the -- this is the first human virus. It came in around 1918. This virus persisted to 1957, the time at which it disappeared, and it reassorted with an avian influenza virus and gave you the H2N2 virus. Four genes from this particular H1N1 virus persisted. Four new genes were entered into the human population.

IN 1968 two new genes came in, PB-1, PA. These are the two virus -- This virus then mysteriously reappeared in the population in 1977. These two viruses now co-circulated. These are the genes that are present now in the human population.

So the question is what gets added by putting -- What genes get added by putting the cold adapted virus -- Okay, and again you can look on this as an example of any kind of live attenuated virus vaccine -- into the human population?

These are the genes that are present. You

have to remember, the H2N2 virus, Ann Arbor virus, is a -- It's an H2N2 virus, and these are the genes that it has. Okay?

Now the only gene -- okay, lineal descendants, this gene, this gene, this gene, this gene and this gene are already present. Its lineal descendants are present in the human population. Okay? So you're not introducing anything that humans have not seen. Humans have seen this PB-2 gene. It circulated in 1957 -- this PB-2 gene, from '57 to '68, and then it left the human population.

Does introducing this particular gene represent a threat? The answer is almost certainly not. This gene is related -- although we give it a nice little black color here, this is 98 percent related by amino acid sequence to the other proteins. It's basically the same gene, no special situations. No special virulence has been associated with this particular gene.

I can see, if you have an individual who's co-infected with a wild type virus and this virus, if you get a wild type virus out of it, that's what you basically could get out of it in that situation. It's a wild type virus that would be circulating -- that could be circulating in the population as well. I

don't believe that it represents a significant risk.

How about in the pandemic situation? Just consider, we have an H5N1 virus appearing in the human population in 2000-something. Okay? At the same time, we have -- these genes are also present in the population. Let's just say this virus appears.s

Now when this particular virus appears, there's a special committee that's been -- that exists, a pandemic planning committee, that will make a decision that this particular virus has shown an epidemic behavior pattern that indicates it is highly likely, almost certainly to come into, to spread and cause a worldwide pandemic.

At that point in time -- okay? -- it would be perfectly reasonable to introduce this particular virus into communities that this virus has not yet come into, because there's a 100 certainty that this virus will appear in that community.

Under circumstances where you have cluster infections that occurred with the swine flue in 1976 and in the H5N1 infection that occurred in Hong Kong in 1997, it is not necessary to, obviously, start -- It would be not recommended by this pandemic committee who has learned by experience that you would not use a virus such as this.

Once a new virus has declared its pandemic potential, it will come into your community, and it will be associated with a tremendous amount of disease. In the pandemic setting, live attenuated viruses offer the greatest opportunity for protecting the human population.

So it would be -- On a risk benefit level, you would go ahead and clearly use this virus under that particular circumstance.

Now these two questions, next two questions, are going to be addressed by Dr. Wright. I'm not going to go into them. I'm just going to conclude my talk with addressing those first three questions.

CHAIRPERSON FERRIERI: Thank you very much, Dr. Murphy. Please stay at the podium. We'll see if the panel here at the table has questions for you. Dr. Greenberg?

DR. GREENBERG: Brian, in your last question, which may be perhaps the most important, at least to me, the question is, once a new pandemic strain has declared its pandemic potential. Are there definitions of what that declaration is other than the committee saying there's a declaration?

That's going to be the key --

DR. MURPHY: Well, okay. No. Obviously, there's no definition for that particular thing, but you would think that the committee would use a variety of types of information, the evidence of spread in multiple geographic locations. This would be a criteria that was not satisfied in either the New Jersey epidemic or the Hong Kong epidemic.

You might -- There might be geographical limits spreading over distances of thousands of miles. I don't know, but it's very clear. You'll know it. When the H1N1 virus appeared in '57, you knew it was going to be coming over here, because it was spreading in a -- like an atomic bomb. It was spreading in concentric circles around the point from which it appeared. The same thing happened in '57, and the same thing happened in '68.

That's the nature of a pandemic virus or a virus which appears in which there's a large percentage of the population is susceptible. There's a point of origin, and then it spreads by -- you know, bi-directionally, multi-directionally throughout the world, reaching 60-70 percent of the population first year, 90 percent by its second pass through the population.

CHAIRPERSON FERRIERI: Dr. Edwards?

DR. EDWARDS: Brian, sometimes it seems that the H3N2 reassortants appear to grow more readily in humans, and sometimes H1N1. How do you explain the variability in the immunogenicity of the cold adapted strains, depending upon what their hemagglutinin and neuraminidase may be?

DR. MURPHY: I simply don't know. Okay? It's as simple as that. I think there is some variability, but the real answer to that is, even though there is some variability, what is shared and what is common to all of these viruses, basically, is what I described to you today.

There are reproducible sets of properties that are conferred by the set of six genes. There's some variability in terms of infectivity, immunogenicity, etcetera, but in general the means and the immunogenicity, etcetera, that is provided is a consistent property of these viruses.

I have no idea why you had the variability, but I do know that you do have the mean and the general set of properties that are transferred.

CHAIRPERSON FERRIERI: Dr. Cox from CDC, do you have anything to add to this point?

DR. COX: You also see variability in the

immunogenicity of the inactivated vaccines, and we don't understand that either. So I don't think it's anything very different from what we're seeing with the inactivated vaccines and differences that you get through having different gene constellations.

CHAIRPERSON FERRIERI: Thank you. Dr. Kohl?

DR. KOHL: Dr. Murphy, thank you for such a lucid description. Can you give us a feel for the time parameters we're talking about in terms of when a new virus bursts on the scene to when it's obvious that it becomes a pandemic potential or declared a pandemic by whatever definition, and how long it takes to gear up a new live attenuated vaccine?

DR. MURPHY: Nancy might -- or Rob might remember this a little bit better, but let's say in 1957 when the H2N2 virus appeared. My recollection is that it appeared around February of the -- It was first noticed in February, and then by the summer, that summer, we started having outbreaks in the United States. Okay?

These were like in August -- July/August, a lot of the -- in Boy Scout camps around the United States, we had severe infections, mortality, etcetera, occurring in kids at camp. So we're talking about a

five-month period of time.

The time it takes to do the old reassortment process and to prepare these vaccines is five or six months. This is one of the reasons NIAID right now is trying to anticipate and set up programs to anticipate the occurrence of pandemic viruses and make seed lots and make master seeds, test them in humans, that can be used in that setting.

The pandemic -- In the interpandemic setting, you generally have -- The system that generally works now would be applied to these. You would make recommendations that new hemagglutinins or neuraminidases would be incorporated into the preparations, but that's what we're hoping for in a pandemic situation.

CHAIRPERSON FERRIERI: Dr. Schild?

DR. SCHILD: Brian, do you want to say a few words about the techniques in the laboratory for selecting these desirable reassortants, natures of the antisera that you might use to suppress the unwanted reassortants and the substrates, cell substrates in which those manipulations occur?

DR. MURPHY: Right. The cell substrates that these manipulations generally have been done primary chick kidney tissue cultures. This virus has

basically been plaqued and cloned and passaged in primary chick tissue cultures, and these are generated from SPF eggs, etcetera.

The antisera -- I don't know what John Massab has used, and I don't know what the company would use, but these would basically be animal antisera made to the H2N2 donor virus that are used, made in an animal, hopefully would be done in an SPF animal, and it would be used in the generation of such viruses.

I think that would be something that the FDA would be very carefully -- would want to look at, and to make sure that, you know, the substrates as well as the antisera that are used for the selection would meet all of the appropriate criteria.

CHAIRPERSON FERRIERI: This is a wonderful opportunity for questions. We have the time, and we have several people at the table who have raised their hands. Dr. Snider, you're next.

DR. SNIDER: Yes. Dr. Murphy, does the cold adapted virus grow in birds? I was just wondering. I would assume it may not, since the temperature is higher, but my limited understanding of influenza is that a lot of the reassortment may be occurring in birds and other animals, not that anybody

is going to go out and vaccinate birds with this, I presume. But if it got into birds, would it be sustained?

DR. MURPHY: No. The answer to that would be, it would not be sustained in a bird population. This particular virus would not be sustained in a bird population, for two reasons.

One is the body temperature of a bird, as you know, as you alluded to, is around 41 or 42. These viruses shut off at 38. They would not be able to grow in the core temperature of the bird.

Second, these viruses are not adapted for efficient replication in the intestinal tract of birds, which is the major site of replication of viruses in the birds, and they are actually spread in birds by cloacal secretions where these viruses appear at titers of 10^8, etcetera.

So I don't think that these particular viruses represent a threat to our avian, agricultural animals.

CHAIRPERSON FERRIERI: Well, that's a very important point to make, though. Not everyone knows that information, I don't imagine.

DR. MURPHY: Maybe Rob would like to comment. You know, he knows a lot more about this

than I do, and he could -- If you want to get another opinion on that, I would suggest Rob might want to comment.

CHAIRPERSON FERRIERI: Dr. Webster.

DR. WEBSTER: I think the point has already been made that the high temperature of the bird would make it impossible for this sort of transmission or reassortment to take place. I'd feel quite reassured for the agricultural purposes that these present no problem.

CHAIRPERSON FERRIERI: Yes, Dr. Kilbourne? And I haven't forgotten you.

DR. KILBOURNE: Well, I think this may be true of the virus itself as it goes in, but what about the genes that the bird may -- the bird's virus may acquire from that virus?

I think Brian himself has shown you can have reversion of even the PB-2 gene on a limited number of hamster passages. So I think the possibility is still there. Although the virus per se, the CA virus, may not be acquired and propagated to birds, certainly, genes might be introduced into the avian gene pool.

DR. MURPHY: I think that is correct, but I think you just have to know that that same

opportunity exists for the human influenza viruses that are currently circulating in the population. These have -- and these have a greater opportunity for gaining access into the avian population, because people actually sneeze and cough when they are infected with wild type viruses, in contrast to this cold adapted virus where there basically are relatively minimum symptoms.

So even though the wild type viruses exist out there, they really haven't presented a -- human viruses haven't presented a problem to our domestic poultry.

DR. KILBOURNE: As far as we know.

DR. MURPHY: Right.

CHAIRPERSON FERRIERI: We'll continue this theme. Dr. Webster?

DR. WEBSTER: Continuing to respond to Dr. Kilbourne, the reverse direction, the transmission of avian influenza viruses into a human gene pool, we know, has occurred twice. Roland pointed it out. Brian pointed it out.

We've looked at other times, and this is a very rare event. The transmission of avian/animal genes into the human gene pool does occur, but it's a very rare event.

CHAIRPERSON FERRIERI: Dr. Breiman, and then Dr. Daum and Dr. Huang.

DR. BREIMAN: Thanks. Dr. Murphy, you had alluded to -- in a pandemic setting, speed may be very much an issue in terms of being able to provide vaccine. There are a couple of questions that occurred to me related to what we're talking about today.

One is whether the cold adapted live attenuated approach would offer a selective advantage in terms of speed or yield from eggs that might be relevant in terms of providing enough vaccine quickly.

I guess the other issue that had occurred to me, too, and it's come up lately, is the question of bio-containment, as you talked about. I wondered about the issue of altering the high cleavability phenotype before providing it to the manufacturer, and how easy that is, whether that's something that can be done in the setting where speed is of the essence.

DR. MURPHY: Absolutely not. I mean, that's one of the reasons why we're trying to work out -- Dr. McGuinness and colleagues at NIAID are trying to do what we would consider an anticipation of this. So that all of the procedures that need to be done and have in place can be anticipated and put into place.

There's no way that this can all be done in the time context that you have at the emergence of a pandemic virus. It's absolutely essential that our institute sort of play a very proactive role in trying to develop the reagents that are necessary for use in this setting.

You had one question that I think I forgot.

DR. BREIMAN: Just the selective advantage of cold adapted virus.

DR. MURPHY: Oh, the viruses don't grow any better in eggs than the inactivated vaccine. Inactivated vaccine -- but they can probably -- It would be likely that they would be more infectious and maybe be able to be used at lower dose.

Currently, there are -- You get approximately -- I could be wrong. Roland, you might know this, or somebody else might know this. You might get two to three doses of an inactivated vaccine per egg.

These viruses, you probably can get something in the order of a magnitude of 20 to 30 doses per egg. So you have a small advantage. The main advantage in the pandemic setting of the live versus the inactivated is its greater immunogenicity

in that setting. That has to be remembered, and that has to be appreciated.

CHAIRPERSON FERRIERI: Dr. Huang?

DR. HUANG: Would you tell us a little bit more about the cold adaptation process and whether the virus is cloned, and what passage levels that you use?

DR. MURPHY: Okay. Now this again was John. John Massab did this. The virus is a cloned population, biologically cloned, not cloned in a molecular sense.

I got to apologize. I forget the exact number of passages. My recollection -- Nancy, you might remember this better, but it's in the vicinity of about 45 passages sequentially going lower temperatures in primary chick tissue, with a cloning at the end to ensure genetic homogeneity.

Then, of course, all of the reassortant viruses that are generated from the donor virus -- okay? -- are cloned -- they would be cloned, biological cloned, in the chick substrates. So that's the best I can say. This is, again, primary chick tissue culture this was all done.

DR. HUANG: Well, knowing what you know now, would it make any sense at all for recreating a cold adapted strain by site-specific mutagenesis and

deletion and making temperature sensitive markers in every segment?

DR. MURPHY: I would -- The answer to that is, you know, it would be fun to try. I've tried that. I've put in three ts mutations into the PB2 gene, and following one passage in hamsters, it reverted.

It absolutely flabbergasted me. I could not believe it. I was, as I'll say, flabbergasted. You can try that. This particular process we are talking about is a 17 year process. Okay? So if you generate a new donor strain, 17 years.

It's going to be a tough project to ask an individual to sort of enter into.

CHAIRPERSON FERRIERI: Dr. Daum.

DR. DAUM: I think sort of along the same lines is something that, not being an influenza person, I'd like you to clarify that, I think, flicked by maybe a little too quick for me.

That is that I think you said that there were six genes that mediate attenuation of the strains. I wasn't clear whether they were all necessary or sufficient, and there was one slide where you talked about reversion of that thing.

I think you were talking phenotypically,

and I wondered --

DR. MURPHY: Yes.

DR. DAUM: -- if each of the six genes had been looked at, and if any of them revert.

DR. MURPHY: Okay. First of all, there are three genes, the PB1 gene, PB2, and PA, have been individually identified as attenuating genes -- Okay? -- clearly and statistically identified.

The contributions of the other genes as individual genes have not been identified as major attenuating. What has not been done is doing a study where you took the three genes such as the NP, NS and N, put it together, and see whether that is an attenuating mutation. My guess is it would be, based on the unbelievable genetic stability of this particular virus.

Now your second question is have viruses been taken out of vaccinees and each of the genes that are associated with attenuation been sequenced. Okay? Is that correct?

You're right about the phenotypic. The phenotypic stability has been checked for the ts phenotype and the CA. These have been maintained. So there really hasn't been a compelling reason to go back and look and understand the genetic basis of

reversion, because we haven't seen that, which is again quite remarkable.

I don't know whether -- Nancy, have you -- Do you know anybody who has sequenced -- done a systematic sequence analysis of viruses that have come out of the respiratory tract of vaccinees?

DR. COX: We really haven't done that for the U.S. developed live attenuated vaccines, but we have done a lot more with the Russian vaccines that were developed by a very similar process, and we've looked very carefully for the markers of attenuation -- or the amino acid changes that were identified in the cold adapted viruses, and they are very stable.

CHAIRPERSON FERRIERI: Thank you. Dr. Patriarca. I'm sorry, you've been very patient.

DR. PATRIARCA: Thank you. Peter Patriarca, FDA.

Brian, thanks a lot. Brian, I have two questions related to the community aspect of this and whether widespread use of these vaccines could pose a public health hazard in terms of, as you pointed out, introduction of new genes into the human population or at least genes that haven't been around for quite a while.

I have two questions related to that.

First, I think that the slide that you showed about what genes could and would be introduced, I thought, was very illustrative and reassures me, at least, that this probably will not pose any kind of a public health problem. But related to that, I'm wondering whether -- When you talk about these genes, you're generally speaking about these in terms of isolation, and I'm wondering whether the introduction of some of these genes could -- whether there could be an interaction between the genes that were introduced and the genes that were in the other wild circulating strain.

In other words, interaction between two genes -- could that confer some sort of virulence that would not otherwise be expected?

My second question that's related to that is whether anyone has done the experiments where they actually created reassortants that would represent potential viruses that could be introduced into the human population and whether those had been tested in animal models, and are they, in fact, still attenuated?

DR. MURPHY: Right. First of all, the single gene experiment that was done where we looked at introducing a single gene in the context of a wild

type virus -- okay? -- mimics this from the Ann Arbor virus -- mimics a situation of introducing at least one of the genes.

This was done as a systematic study, first of all, and every one of the reassortants that was tested and made in that context was either less -- had less replication in an experimental animal or was equivalent. Okay, that's one.

The introduction -- The possibility of recombination of viruses -- okay? -- is going -- It's occurring now in the human population with genetic exchange between the H1N1 and the H3N2 viruses. Now there was a nice paper that Roland selected to hand out to the Committee which describes the particular reassortants that have appeared in the human population, and Roland indicted in his talk that such viruses, although they've appeared and sometime have appeared and been isolated under several different years -- you know, you could see the same virus, suggesting that it might have epidemiologically spread. It actually died out. It did not become a predominant, had no unusual properties that existed.

So reassortment will occur. Okay? It has occurred between wild type viruses. Okay? It's been documented, but nothing unusual, unexpected has come

from such genetic exchange.

Nancy, would you have any information in addition to that?

DR. COX: We don't -- We have just a bit of unpublished information. We've just documented another instance of reassortment between H1 and H3 viruses in China. We're still attempting to sort out the origin of all of the genes, but there has been another reassortment. But in each case where we have documented reassortment between H1 and H3 viruses circulating among humans, we have seen no increased virulence or other unusual properties, and in each case in the past those viruses have not persisted in nature and have died out.

So there doesn't seem to be a selective advantage to those reassortment events so far.

DR. MURPHY: Right.

CHAIRPERSON FERRIERI: Dr. Kim, and then Dr. Kohl.

DR. KIM: To, I guess, make the story a little bit complete, I just want to find out whether there is any -- has been any change as a result of a attenuation or combination of a genetic elements susceptible to antiviral agents.

DR. MURPHY: The only antiviral agent, I

think, right now that's licensed in humans is amantadine. I think the cold adapted virus, as far as I -- ramantadine. I believe that the H2N2 virus is fully susceptible to amantadine and ramantadine, but I'm not absolutely certain of that.

Is the answer yes to that? Okay.

CHAIRPERSON FERRIERI: Dr. Kohl is next, then Dr. Webster, and then we'll have to close the question and answer period.

DR. KOHL: I'm still fixated on the time frame and the pandemic scenario. Let's say there's an H11 floating around in a Chinese chicken, and you'd like your people to be prepared proactively with a strain ready to roll.

What's the odds that you will pick up a heretofore unseen hemagglutinin in Chinese chicken and have that ready to roll when this thing bursts on the scene? How much of a surprise are these strains?

DR. MURPHY: Okay. You know, obviously, it's a very good question, an important question. The history of influenza virus in humans is that there is cycling of the viruses in humans. The only viruses, really, that have appeared in humans and have been maintained in humans are H1s, H2s and H3s.

So that's the experience to date. So the

question is can other viruses gain access, too? The only real experience we have, in addition to these, is what occurred in Hong Kong. Clearly, H5 virus can infect and do tremendous damage in humans.

The answer to the question is I think that, if you were being for completeness, you would probably want to make representative strains from H4 through H15, but the government doesn't -- you know, doesn't have unlimited sources of money, etcetera.

So what they would do is they're getting a committee together to try and select out particular strains that would represent specific threats. I'll give you some examples. H5 would certainly be a category, H7 which has a highly cleavable hemagglutinin.

H2 virus right now we should be prepared for, because that virus has not circulated in the human population since 1968, and everybody under the age of 30 is basically fully susceptible to an H2, virus with an H2 hemagglutinin, and that there are other selected viruses that might be chosen based on epidemiological patterns in animals, what viruses are appearing in pigs, etcetera.

So what we're doing now is sort of making a priority list of hemagglutinins and then we're going

to -- we're planning -- I hope that we maintain the resolve to go through and identify select hemagglutinins, make candidate inactivated vaccines, candidate live attenuated virus vaccines, and do the clinical trials to see whether the set of properties that I exhibited up here for the live attenuated virus can also be seen with viruses bearing quite distinct hemagglutinins from the ones we've tested.

I hope that answers your question.

CHAIRPERSON FERRIERI: Dr. Webster.

DR. WEBSTER: Brian, I want to return to the same theme, the H5N1 in Hong Kong. One of the saving graces there was that the H5N1 in humans wasn't transmitted form human to human.

DR. MURPHY: Right.

DR. WEBSTER: Now if we had been using a cold adapted virus at that time, and given that the nuclear protein in some of the other genes that we know about are involved in permitting host range transfer, and that is not a ts characteristic of the virus, would you be happy, comfortable, in using a cold adapted vaccine in the face of this emerging situation?

DR. MURPHY: Would I -- Are you asking me, if I had a cold adapted virus in my hand, would I give

it to individuals who are having a -- who are being seeded by H5N1 viruses?

DR. WEBSTER: No. If the cold adapted vaccine was used -- being used in the world and was being used in Hong Kong, because that's the time when it might have been used, and this emerging situation occurred.

DR. MURPHY: Now this is a very important question, and I don't have an answer for that. Okay? I do not have an answer for that, and I don't think there is an answer for that.

You know, the answer for that, Rob, is that wild type viruses are going to be circulating. That system, that situation, will reproduce itself at some point in time with the naturally occurring wild type viruses.

Should we be denying the benefit of a virus -- an immunization procedure that has the possibility of protecting, to the extent that it's a cold adapted virus, for the possibility of generation of a reassortment and in a very unusual situation?

My answer to that is this is a complicated question that a committee like this would have to make their judgment on. I would go ahead and use this virus vaccine, knowing that that particular situation

can occur with the wild type viruses, and it is a risk. It's a risk that we would have to make a decision on whether to take or not.

CHAIRPERSON FERRIERI: Operating under the principle that one more question won't kill us, Dr. Hall, one last, brief question.

DR. HALL: Yes. One of the questions was what Dr. Webster was asking, the difference in potential infectivity between the wild, the H5 and if it were in a reassortant. But the other thing in the transmissibility -- You mentioned, Brian, that the reassortant virus is likely -- unlikely to be transmitted, because the shedding is about 10^3 and a HID-50 of about 10^5 for an adult. But the child, the HID-50 may be at 3 or even less than that 10^3 or so.

Is that -- What do we know about the transmissibility then in the young, unprimed child?

DR. MURPHY: That's a very good -- That would be -- As you know, being a pediatrician, if a virus can spread, it will spread in a dayroom setting, and that's the best place to look at that particular question.

Peter Wright has a tremendous amount of experience giving these cold adapted viruses in exactly that setting, and maybe if the Chairperson

doesn't mind, I would refer that question to Peter.

CHAIRPERSON FERRIERI: Do you have an answer, Peter?

DR. WRIGHT: I'll answer it in the course of my -- I'll give you the information we have in the course of my presentation.

Basically, the short answer is we have not seen transmission in young seronegative children, either in the family setting or in the daycare setting.

DR. HALL: Is there any reason to think that the survival of this virus in the environment is any different than the wild virus?

DR. MURPHY: No, I think it would be -- I think you could consider it being comparable to the wild type virus. It would be reasonable.

DR. HALL: In terms of fomites is what I meant, you know.

DR. MURPHY: Right. You have to remember that it's starting out at a lower titer than the wild type virus. So the time that it gets down to a noninfectious level would be sooner than wild type virus, but I don't think it has any special problems that would -- properties that would alter its rate or kinetics of inactivation.

CHAIRPERSON FERRIERI: Thank you very much, Dr. Murphy. We won't have many minutes for questions for Dr. Wright, but we'll do the best we can.

The next presentation, clinical studies with live attenuated vaccines, by Dr. Peter Wright from Vanderbilt. Would you like someone to assist you in putting on your transparencies?

DR. WRIGHT: Perhaps. I initially declined, but perhaps --

CHAIRPERSON FERRIERI: I think that would be more efficient, Peter. We all wear many hats, as you know, both here and at home.

DR. WRIGHT: Perhaps it will in terms of my being at the microphone. I appreciate the opportunity to speak to you.

I'm going to limit my discussion very largely to the questions posed by Roland for the Committee, so that I'm not going to address in any extent questions of efficacy nor really review in great detail the very large clinical experience with this vaccine.

When the question was first posed to me of reviewing this, I really had nightmares of trying to go through what is a very, very large database of

overall safety. So I'm going to focus initially on just a few issues that relate to safety and relate to the kind of symptoms that might be seen with the live attenuated vaccine that might, in turn, have implications for the questions asked, and then go rather more specifically to the questions.

If we can have the first overhead, Roland.

I'm putting this up for two reasons. I'm going to present one table on the clinical symptoms associated with wild type influenza in young children, and I'm also going to point out that this, I think, was the first paper that pointed out protective efficacy of a live attenuated vaccine and point out that the date was 1977.

So perhaps this vaccine that -- we've heard various accounts of how long it's been in preparation, but we've known at least now for 21 years that this is a vaccine that could protect against influenza.

We can have the next slide, and concentrate on the issues here. These are the clinical observations in 24 seronegative children. I'll show another slide briefly later that has a slightly enlarged number, but just to say when you isolate influenza from children, they will be very

symptomatic, and this in turn is different than what we'll see with the cold adapted vaccine.

So that virtually all have fever, cough, low grade fever and cough, and over half of them, 13, had fever greater than 103. In terms of secondary bacterial infection, you have with naturally occurring influenza in young children no trouble at all demonstrating associated otitis or pneumonia, six children out of 24. So a quarter of the naturally infected children had either otitis or pneumonia.

We went through -- WE collectively went through a very large number of Phase I trials in children and adults, and if we can have the next overhead, the first large study was one that Kathy Edwards did.

This was a trial in individuals 1-65 years of age, and involved 5,000 individuals receiving something in the order of 12,00 doses of vaccine divided between placebo inactivated and live attenuated vaccine. These vaccines were given repeatedly over a four-year period.

If we can have the next slide: Again I'm going to concentrate on this particular table. If it's hard to read from the back, I will point out what, to me, are the only things that I really want to

emphasize.

That is that, if you give the vaccine to a large enough group of people, you will see the emergence of a significant association of sore throat, coryza and lethargy, and a lesser but still significant association with headache and muscle ache in the group receiving cold adapted vaccine as compared to control.

I can point out that one will also see with inactivated vaccine local reactions in excess of those seen when a placebo is given intramuscularly.

We can have the next slide. We now come to at this point the seminal paper in our understanding of the potential of the live attenuated vaccine published with Dr. Belshe as the first author, a group assembled by the manufacturer of the vaccine and, most importantly, by NIAID which provided a great deal of the support for the conduct of this trial.

We can have the next slide. Again, I want to concentrate here on clinical symptoms, and what you will see is very similar to the observations in the broader age range that Dr. Edwards studied, this involving children 15 to 59 months of age.

Again, in the first several days after administration of the vaccine, there was excess

rhinorrhea and nasal congestion that reappeared on about day eight or nine, and there is one day in which there was an excess of fever. But these are, I would present, very much milder symptoms, and really the clinical assessment of these symptoms would be that they were very tolerable, and I don't think that anybody in consideration of the vaccine has thought that these minor upper respiratory symptoms would form a contraindication to the administration of the vaccine.

They do, however, perhaps raise the question of associated bacterial infections in some of the specific questions, and that's my major reason for presenting them, not to, in a definitive way, review the overall data on safety of this vaccine.

So if we can go to the next slide, and we'll start at the top. I want to come back to my assessment of the implications for transmissibility and reassortment of attenuated and wild type influenza, and to point out, as has already been pointed out, that in a variety of settings reassortment can be seen.

Reassortment can occur between wild type influenza strains. This has already been commented on. The particular paper I'm quoting is one that Dr.

Kendall and Cox had in a symposium, and it's obviously felt to be important in the emergence of novel strains by shift, either in man or in animal reservoirs.

Reassortment has also been documented during the simultaneous administration of bivalent A, H3N2 and H1N1 cold adapted vaccines. That's work that we did, published in Vaccine, and in fact the reassortment occurred, to me, still at a strikingly high level when one considers that simultaneous infection of a single cell is necessary to demonstrate reassortment.

We were, by enzymatic characterization of the neuraminidase and by classical methods of characterizing the hemagglutinin, able out of 212 plaques picked from young children shedding virus after having been given a bivalent H3N2, H1N1 preparation, demonstrate H3N1 plaques and H1N2 plaques. In fact, the overall percentage of reassortments in the total plaques characterized was 25 percent.

Reassortment at a lower level, eight in 340 clones -- and this is work done by Dr. Younger, Dr. Treanor and Dr. Patricia Whitaker-Dowling; Dr. Younger and Dr. Dowling are here -- demonstrate that when they gave a cold adapted and live -- this is a

wild type H1N1 -- that the only virus recovered had a wild type phenotype.

So they gave a cold adapted and a wild type virus simultaneously. This was an extension of some work that they had done in tissue culture and in animal models, demonstrating that the cold adapted vaccine appeared to have a negative dominant effect over wild type virus, and it would out-compete wild type virus.

They characterized the internal genes and found reassortment at a lower but still significant level and, as I say, this study was done to explore the concept that the CA vaccine can be dominant over the wild type virus.

The co-administration of CA and wild type virus in this particular case did not lead to significant decrease in illness, but the study was small in number, and they point out a number of the limitations of the design of the study in actually demonstrating this fact.

This remains, I guess, at least a potential for the cold adapted vaccine in the face of the established epidemic that not only will be more immunogenic, but one may see an effect of vaccine more rapidly after administration, perhaps even within

days, than is seen with inactivated vaccine.

I next turn to the case of the Mongolian camels. This is a report of Dr. Schultacek, and in Mongolia a PR-8 virus reassortant was used as a partially UV inactivated vaccine in 1978. I don't know the whole history of this.

What he has demonstrated is that a PR-8 virus has continued to circulate in camels and children in Mongolia, and to demonstrate reassortment with other strains. So this is an example where not the cold adapted vaccine that we're talking about here but apparently an incompletely inactivated vaccine introduced a variant hemagglutinin and other genes into the population.

They also pointed out that in Mongolia this has been accompanied over roughly, I think, from 1978 to 1991 by very little antigenic drift, and raised a question in the article of maybe this 1950s H1N1 virus wasn't in the freezer, but they propose, although I'm not sure that I understand the mechanism, that in populations with very low density there may be long term circulation of virus with very little antigenic change.

So these are the examples, that I'm aware of, of reassortment occurring. It can occur.

Reassortment, as has been pointed out, between the cold adapted vaccine and a wild type virus would likely attenuate the resulting reassortant virus, as the CA attenuating mutations are in several genes, and Brian has already made this point.

Maybe we can move it up a little bit, just for the people in the back, almost through this page.

The evidence against virus transmission, either between young children in the family or daycare center, is really -- although limited number, is quite strong. So that the reassortment would likely have to occur in the vaccinee. I think that the changes of this virus being transmitted to other people is small.

If we can have the next overhead, we will demonstrate what I'm aware of as the available information.

The information at the top is from the large trial that Dr. Belshe reported, and the data was shared by him and by Mark Wolfe, the statistician. So there were a fair number of seronegative vaccinees who had antibody rises, and there were seronegative family contacts identified, and none of the family contacts -- the numbers you can see here -- had a serologic rise.

In addition, we went back through our data

in Phase I studies at Vanderbilt with seronegative placebos in close daily contact for usually a ten-day period, with vaccinees shedding CA vaccine. So we only took studies in which seronegative placebos were identified in which vaccinees had clearly shed virus.

Some of these studies were done with either monovalent or bivalent A viruses. Some of them were done with trivalent, which would have a B component.

So you see the numbers here. There were two people in whom we recovered virus on either one or two days. Neither of these experienced an antibody rise, and I think it is conceivable that they were infected. We isolated virus from them, but could not confirm it by antibody rise, and in general in young children the concordance demonstrating infection and demonstrating an antibody response has been very high.

Furthermore, I think by analogies with some of the thinking that's going on with live attenuated polio vaccine now and its potential to continue to circulate, even if occasional circulation occurs, this virus falls very well below the threshold that is necessary to sustain circulation through -- sustain transmission through more than an immediate contact, and there are rules that have been developed

in terms of making a decision about whether any kind of sustainable transmission may occur with a live attenuated vaccine, and this would certainly, by my estimation, fall well below that.

So I would contend that the lack of transmissibility of the CA virus virtually eliminates the risk of spread as a result of vaccination. There is some work currently ongoing -- I really cannot comment on the number of individuals or results -- looking at the safety of live attenuated vaccines in HIV-infected volunteers.

There has not, to my knowledge, been extensive examination of the vaccine in other immunocompromised individuals. The HIV population is perhaps the population most likely to be unidentified and to be considered a candidate for vaccines, although the current screening techniques in the United States are really very efficiently identifying most or a high percentage of HIV infected children.

Reassortment as a result of simultaneous infection with CA and wild type virus can occur, but would confer no selective advantage, and the only scenario which we've already raised in which concern would be raised would be the transfer of a novel H or N gene from attenuated to wild type virus by

reassortment.

This would be a setting in which the novel genes had been introduced in CA vaccines in anticipation of an epidemic that did not materialize, and I think, Brian, this is obviously something that all of us are concerned about, and Brian has talked a bit about what the guidelines might be for the introduction of a live attenuated vaccine.

So that is my take, if you will, on these questions. So we can go on to the next overhead.

We'll talk now about the damage that influenza can cause to the epithelial surface. Wild type influenza causes loss of ciliary activity and de-epithelization, which leads to increased bacterial superinfection in the upper respiratory tract with otitis and in the lower respiratory tract with pneumonia.

The paper that I talked about from our group is one of only, obviously, many, many that has documented that.

The association of influenza infection with otitis media has been made on many grounds, certainly on a epidemiologic basis, by the observations of protection from otitis media provided by both inactivated and live attenuated vaccines, by

changes in middle ear findings on experimental wild type challenge in adults, so that Dr. Hayden's group at the University of Virginia has been doing studies in which they can quite consistently find, at the very least, changes in middle ear pressure and occasionally frank otitis during the course of wild type influenza virus challenge.

To my knowledge, these sort of detailed studies of middle ear pressure have not been done in adults during cold adapted vaccine. They could be done, but I will make the point at the end that I think they would not be terribly informative or terribly likely to show otitis.

Influenza replicates in cells lining the respiratory cavity, and studies in isolated primary epithelial cells is an area that we're interested in, that Dr. Couch is interested in. We are now trying to study in more detail the subtype and the extent of damage caused in this system.

What we can say is a growth of live attenuated influenza A and B cold adapted vaccines in primary epithelial cells, as it is in man, is hundredfold less than wild type virus. Actually, that finding of a limited growth of attenuated respiratory vaccines has extended in our hands also to live

attenuated respiratory syncytial virus and parainfluenza-3 virus vaccines.

Administration of live attenuated influenza vaccines is associated with a slight increase in upper respiratory symptoms in children and adults, but no increase in otitis media. This seems to me to be the most discriminating way of looking at this question of whether secondary bacterial infection may occur with a cold adapted vaccine, and I'll show you these tables in just a minute.

We don't think that there's any possibility of secondary bacterial pneumonias, if only because all of the evidence from the shutoff temperature of the vaccines, the temperature at which the vaccines will grow, and the absolute lack of any association of lower respiratory symptoms, even cough, with administration of the vaccine suggests that its replication in the lower respiratory tract is either nonexistent or very, very limited.

There was an article distributed in the infant rat model in which wild type H3N2 strains in the neonatal rat were associated with a facilitation of bacteremia and meningitis due to H-flu, and there was some data in that table on the -- in that paper on the cold adapted vaccines, and I've summarized that on

the table.

So maybe we can go to the next overhead, and then I'll come back to the conclusions.

So the studies of H-flu bacteremia in the infant rat, an interesting model developed primarily to look at systemic H-flu disease and a model in which not getting bacteremia is dependent on dose, demonstrated that, with the addition of wild type -- these are two different H3N2 strains -- you could quite frequently get bacteremia and meningitis, which otherwise you would have to give a higher dose of the H-flu to get.

The cold adapted vaccines, although there were perhaps one instance in which bacteremia was demonstrated, did not cause meningitis, and a very similar experience in my summary of the table in that paper is seen with the A/Victoria where again bacteremia in combination with wild type influenza was common, and meningitis was seen with a cold adapted vaccine. There was very little evidence for either of these bacterial invasions.

The data, again courtesy of Mark Wolfe at Emmis Corporation, in terms of the episodes of febrile otitis documented with a physician's visit in the ten days after vaccination -- and I've also seen the

information for ten to 42 days after vaccination.

This was a two-year study. In Year One two doses of vaccine were given. A single dose was given in Year Two. This is the trivalent cold adapted vaccine, and no significant increases in otitis in vaccinees were seen either with their very first dose or vaccine, their second dose in the same year or a dose in the next year.

So this -- if we can go back maybe to the conclusions. It would seem to me that live vaccine internasally would carry a low probability of sustained epithelial damage, primarily based on the lack of association of administration of live attenuated influenza vaccines in young children with otitis media, based on the detailed daily studies, in some cases with pneumatic otoscopy and tympanometry that we performed in Phase I studies, and the much larger database and discriminatory power of these large Phase III studies.

Experimental models for influenza challenge and monitoring of middle ear status exists in adults, but the limited replication of virus in adults with prior exposure to related influenza strains, I don't think, would make the latter a very discriminatory model. They are simply not going to

replicate enough virus to, I think, learn very much from that, although that's something the Committee could consider, and it's not a hard study, basically, to do.

The restriction in the growth of the cold adapted vaccine in the lower respiratory tract makes the possibility of pneumonia very low, and primary epithelial cells have shown limited growth with all live attenuated respiratory vaccines evaluated, and may be a model for screening newly introduced variants.

I do have one -- you can go to the next slide. I do have one growth curve comparing the growth in MDCK in these primary respiratory epithelial cells derived from adenoidal tissue, and you can see that the wild type H3N2 grows above six logs, the cold adapted below four logs, wild type H1 slightly less growth but again a two log reduction in titer with a cold adapted vaccine, and the same seen with the B.

With the exception of the wild type H1N1, this virus grows as well in these primary epithelial cells as it does in MDCK, and you actually don't see in cold adapted -- with a cold adapted the differentiation in MDCK that you do in human tissue of

epithelial origin that has representation in ciliated cells used in producing cells and is representative, I think, of -- as a closer representation of what goes on in the nose as we can get.

So we'll go to the next overhead, and go through at least my assessment of this question of hypersensitivity reactions to influenza vaccine.

Egg allergy is reported to be common in childhood. Estimates of .5 percent, but much rarer in adults, although you do find individual adults who are extremely sensitive to ingested eggs. It's directed both against egg yolk proteins and egg white, ovalbumin ovomucoid, perhaps more to egg yolk proteins in the assessment of an allergy to ingested eggs.

Inactivated influenza vaccine produced in embryonated eggs contains measurable amounts of ovomucoid, ovalbumin. These are the amounts in a recent paper just published in The Journal of Pediatrics from one manufacturer.

A group at Johns Hopkins and the University of Arkansas had identified a group of egg allergic subjects documented by history, skin test, and/or a reaction to oral challenge, including a number with anaphylactic reactions to ingested egg.

All of these individuals were given

inactivated influenza vaccine intramuscularly without any adverse reactions, including those with the history of anaphylactic reactions; nor was there any good correlation of skin test reactivity with any reactions with the influenza immunization.

This same group had done a study of MMR, which contains probably much less egg protein, but does contain egg proteins in that it's grown in chick embryo fibroblasts, the measles and mumps component, and again there was no -- There were some adverse reactions seen, but absolutely no association with a history of egg allergy.

The recommendations for both vaccines was that it could be given to egg allergic subjects without skin testing or other than the usual precautions for anaphylactic and reactions that would be common to any physician's office or setting in which vaccines were being administered.

Now that's not the recommendation of the Red Book, but just to say that the actual injection of egg protein, although in smaller amounts than would be contained in the live attenuated vaccine, has been well tolerated by a group of individuals well documented to be egg allergic.

There is a literature on using

aerosolized, small particle ovalbumin to sensitize the airway of mice, and I would point out that the cold adapted vaccines have been given either by nose drops or large particle aerosol which specifically is designed to exclude penetration into the lower airway.

So there is this model that exists, but in discussion with an individual at Vanderbilt who is working actively with this model with the respiratory syncytial virus, he said that in virtually all investigators' hands, it must be preceded by an intraperitoneal priming with ovalbumin. So just giving repeated doses of ovalbumin to the mouse without intraperitoneal priming is very unlikely to lead to sensitization.

There is in the literature a paper on IgE and IgG binding in proliferative epitopes ovomucoid described in egg allergic patients, and there was this interesting report that was sent to the Committee documenting allergies to an extensive, prolonged inhalant exposure to aerosolized egg solution in a bakery.

Basically, some meat rolls were being sprayed with a high pressure, I presume, relatively small particle generating spray, and it was said that it could be readily appreciated in the environment

that egg was being sprayed everywhere, if you will; and a high percentage of the individuals developed some respiratory symptoms associated with this exposure.

All immunoprecipitants were to yolk components and none were to ovalbumin, and this seems to me to have been an exposure that was really both quite extensive and different than I would -- than I visualize the exposure with the vaccine.

This is a point that I made, that delivery to the lower respiratory tract is really very small. We have looked at this in primates with using technetium sulphur colloid and scanning, and I know similar studies have been done in more detail by the manufacturer of the vaccine, and at least by this technique you really cannot demonstrate any particles getting into the lung, although you do find that 30-40 percent of the dose ends up being ingested, ultimately runs down the back of the throat and is swallowed.

That's a bit higher if you do it by drops, but that's true both by spray and by drops.

Certainly, the live attenuated vaccines, as they're currently prepared in embryonated eggs, would have large amounts of egg protein. They are basically, as I understand the final product,

predominantly in egg allantoic fluid.

I would point out that no immediate allergic manifestations have been reported, including in the largest series of yearly immunizations, the 12,000 immunizations that we talked about, nor in the larger studies that I'm aware of that have been done by the manufacturer.

Live attenuated influenza vaccine has been given to a small number of asthmatics at Vanderbilt without alteration in pulmonary function, work done by Dr. Gruber, a colleague, and my understanding is that Aviron has studied a number of additional asthmatics, again without finding any evidence of altered pulmonary function or lung reactivity.

We in several studies have given patients with cystic fibrosis live attenuated influenza vaccines with -- who had existing respiratory compromise, sometimes quite marked, with no adverse reactions.

So I think we're now -- Is there one more kind of conclusion to this section, and then I am finished.

So my conclusion would be that the delivery of egg allantoic fluid into the upper respiratory tract would seem to carry a lower

probability of hypersensitivity reactions.

People with egg allergy can be identified and could be challenged. However, there is no evidence from other vaccines that hypersensitivity corresponds with allergy to ingested eggs.

Obviously, some consideration could be given to lowering the concentration of egg protein by putting the vaccine in another excipient, and this might be considered in the manufacturing process.

So this is, obviously, my personal assessment of the questions that were posed, and I'm happy, with time permitting, to answer questions and, if not, people can ask me or digest what I've said.

CHAIRPERSON FERRIERI: Thank you very much, Peter. I had a question for you, a general one, without referring to any single product, and it's tangential to your presentation. But given information that there's lesser replication of the attenuated live virus in adults, is it your understanding that the immunogenicity is unaltered in adults compared to children? So the antibody take --

DR. WRIGHT: No. The immunogenicity in adults, I think, almost certainly is altered and is lower, and the best evidence for that is really the study that Dr. Edwards did.

I think -- So the immunogenicity is lower than that seen with the inactivated vaccine, if you simply look at HAI serum antibody titers.

CHAIRPERSON FERRIERI: How does that translate in terms of protection then?

DR. WRIGHT: It's a complicated story. I think the best summary of it or the aggregate would be that the two vaccines over a four-year period against two H3N2 and two H1N1 epidemics in successive years was virtually equivalent -- was equivalent in terms of virus isolation.

There were more antibody rises associated with illness seen in live vaccine recipients. Some of that may have related to the fact that with inactivated vaccine there was already a high preexisting antibody, and demonstration of antibody rises in that setting, we think, is more difficult.

Kathy may have some -- anything that she would like to add. I think the overall conclusion, which was perhaps a bit disappointing at the time, was that the two vaccines behaved equivalently.

Several changes have taken place in the product since that study was done that may influence its immunogenicity and efficacy, and the major one, and really the major one, is that the vaccine is now

being given as a large particle aerosol instead of drops.

It would appear that immunogenicity of the vaccine is slightly better at least when given by this route, which may lead to a more uniform distribution of virus in the upper respiratory tract.

CHAIRPERSON FERRIERI: Thank you, Peter. We have time for one question before the break. Who would like -- Carol, and you've been so nice about not always getting your hand recognized when you first put it up. Please.

DR. HALL: Peter, thank you very much. It was an excellent summary, well done.

I just wanted to mention that, first of all, I think you've given us very good evidence that the use of these vaccines would be effective in preventing the secondary bacterial infections which are of great concern. But in children most of this is probably related to the upper respiratory tract, the otitis and sinusitis, etcetera, and in terms of hospitalization that one of the potential advantages of this vaccine may be the prevention of pneumonia, which is not secondary bacterial pneumonia.

In other words, in children it's different than what's generally described or what Roland

described as the primary viral pneumonia, but most of these children are admitted with a general interstitial viral pneumonia that may be indistinguishable from RSV.

The suggestion would be that, since it does not grow there, that that is the major case of hospitalization, I think, in young children would be prevented. Would you agree with that?

DR. WRIGHT: Yes, I would certainly hope so. People can correct me if I'm wrong. I think that the specific endpoint of lower respiratory tract disease has not yet been addressed in the studies. Paul, I might ask if -- I mean, the protection is against febrile influenza illness, against otitis, with its representative live attenuated vaccine.

DR. MENDELMAN: Bob Belshe presented it --

CHAIRPERSON FERRIERI: Excuse me. Your name and place?

DR. MENDELMAN: Sorry. Paul Mendelman from Avron, Mountain View, California.

In response to Peter's question, Bob Belshe presented the year two efficacy data for the pediatric protective efficacy trial at ICAAC on September 27th, and in Year Two where A/Sydney was the predominant strain, there were eight cases of lower

respiratory tract illness which were either pneumonia or bronchitis or significant wheezing episodes, and all eight cases were in the placebo group.

CHAIRPERSON FERRIERI: Thank you. We have time for a very brief question from the panel. Dr. Kim.

DR. KIM: One question. From the summary data regarding Dr. Belshe and from Vanderbilt Phase I studies, this question relates to the issues which Caroline Hall raised earlier. It's that you indicated that transmission was almost negligible based on looking into the population of seronegative family contacts or exposed placebos.

Was there any children being included or this is just the general population, including children and adults?

DR. WRIGHT: No. All of the data that I presented, in contrast to what Brian presented, was from young children who had never experienced influenza before. So I think in children you do have this question of you're really approaching the infectious dose.

This is something that we saw with the rotavirus vaccine as well, that it was not transmitted, and this we think of as a classically

easy to transmit virus.

So I guess a hypothesis might be that, having symptomatology associated with virus shedding facilitates transmission, both with rotavirus and -- So the fact that these children were not sneezing and coughing may have contributed to the lack of spread in that they had really very minor symptoms.

I would submit that the same might be true with the fact that the rotavirus vaccine does not spread substantially.

CHAIRPERSON FERRIERI: Thank you very much, Peter.

We'll now break and resume our meeting at 10:20. Thank you very much.

(Whereupon, the foregoing matter went off the record at 10:07 a.m. and went back on the record at 10:28 a.m.)

CHAIRPERSON FERRIERI: I'd like to reconvene the meeting, if the Committee members would please return to the table. People in the hall could please be brought in. Please come to the table and resume seats in the audience.

We always take a little more time than we say we will, but I usually know what effect that will have on the rest of the program, and I think we're in

good shape and can give adequate attention to all of the questions posed for the Committee by Roland Levandowski.

First, we'll start with the open public hearing, and for that I'll turn it over to Ms. Cherry.

MS. CHERRY: Now that the presentations have been heard, is there anyone that wishes to make a statement?

CHAIRPERSON FERRIERI: Okay, this is the formal open public hearing session, but seeing no one, we'll proceed with the program. Thank you, Nancy.

I would like to remind the Committee before we return to Roland and his issues for discussion that this is an overall approach that we are examining. We are confining ourselves to the specific issues raised by FDA for us, and even though some of our questions were rather tangential at times, those are not the things that we are being asked to address today.

So, Roland, could you please begin, and also nudge us, if you think we're not being sufficiently targeted.

DR. LEVANDOWSKI: Okay. Well, thank you. I don't actually have any further comments at this point, but I think we would like to hear the

Committee's discussion. There have been -- Even the questions that have been asked this morning, I think, were illuminating and very helpful for all of us to hear, but we do want to have the Committee spend as much time as possible on these issues.

So all I'm going to do, I think, is to put the overhead up here that reiterates the questions.

CHAIRPERSON FERRIERI: Yes, please, and then I'll take them one by one, and we should be able to deal with them.

The first issue for discussion by the Committee, and I would encourage all of the invited participants who are not regular members of our Committee to contribute to this -- we need your input as experts in this area.

The first question is to comment on the markers used to predict the attenuation of live attenuated influenza virus vaccines.

I'll entertain anyone who wishes to lead off. We've heard about these markers regarding the -- that are phenotypic in nature, specifically the temperature sensitivity, the cold adaptation, and the 6/2 gene constellation, and the attenuation in rodents and ferrets that has been studied as well.

So are these adequate markers to predict

the attenuation and the ongoing maintenance of attenuation? Who would like to -- Dr. Greenberg, please.

DR. GREENBERG: I guess Brian would be the person to readdress this. Was it your feeling that, if you were going forward, that there's enough data in the past that you can be sure of attenuation if you have a 6/2 constellation with any new influenza and a cold adapted and ts phenotype, or do the animal markers also need to be done for any new virus that you create?

CHAIRPERSON FERRIERI: Dr. Murphy?

DR. MURPHY: Briefly, we've never -- We've never seen a virus, basically, that had the ts, ca and 6/2 gene constellation that didn't behave in a reasonably predictive way, with some of the variability that we talked about before.

So that's the data. I think there probably are -- I think I discussed 11 in my talk. Since I've stopped working on these viruses, there's been at least probably seven or eight more that have been studied, well up into double figures now.

I don't know of a circumstance that we have not achieved a predictable phenotype. That's the best I can say.

CHAIRPERSON FERRIERI: Thank you. Yes, Dr. Schild?

DR. SCHILD: This has been a very long term project. I remember it many years ago, probably 25 years ago, getting off the ground, and I think those involved should be congratulated on the quality of the work and the long term commitment and the imagination.

As Brian Murphy mentioned to us at the beginning, this approach involves a strategy, not just a "one of" licensing of a vaccine. We've heard a lot of very good information on the stability of the temperature, the temperature adapted phenotype, which is very impressive. However, given that this is a strategy and that currently, based on epidemiological surveillance, strain characterization and so on, there seems to be a need to change the composition of influenza, trivalent influenza vaccine at least once a year.

The question does arise, how much clinical information is going to be desirable in relationship to the testing of each successive new vaccine composition? We haven't actually heard very much of that.

We've heard a lot of impressive historical

data. I think that would be an important issue to discuss.

The other thing I would -- I think is quite interesting is that, although we know that there are three of the genetic components of this virus which are relevant to the attenuated phenotype, it's not quite clear to me the extent to which we know the point mutations in those genes that do concern the attenuation fully, and to the extent to which we have studied the long term stability of those genetic modifications on passage, on long term serial passage.

The evidence that the phenotype is maintained on passage is good, but what about the genotype? I think those are still interesting questions.

CHAIRPERSON FERRIERI: Yes. Thank you, Dr. Schild. I had hoped someone would press on the genotype. Brian, would you like to take off on this challenge?

DR. MURPHY: It's a very good question. The second question I'll address first regarding the genotype.

The only point mutation that's unequivocally been identified with a phenotype that's been conferred by the cold adapted virus is the point

mutation that exists in the PB-2 gene, because it has been possible to take that particular mutation and transferred through a process of reverse genetics into another virus, and then to show in this other virus or in another background it was able to confer a ts and attenuation phenotype.

Now so that's one amino acid that is unequivocally known to be associated with a phenotype. The reverse genetic systems for all of the other genes do not exist at this point in time.

So I think we have to wait, to some extent, until we get that information.

DR. SCHILD: Would that be an area of high priority for future research?

DR. MURPHY: I would say it would be an area of priority. I think we are always much better served when we understand the genetic basis of attenuation of viruses, and then you can look at those particular elements during all phases of manufacture and production and testing in humans.

So that I would agree with you. We should seek that, and I really hope that the basic scientists who are doing that generate the systems that permit the efficient expression of all the other genes of influenza in our reverse genetic system.

Regarding your -- So I think that needs to be done. Regarding the limited -- the quantity of experimentation that needs to be done on an annual basis, I don't know whether -- You know, with this particular virus or viruses in general. Is that what you mean? See, that's a complicated question, whether -- I want to make sure the Chair wants us to get into questions related to the cold adapted virus or to talk in general about --

DR. SCHILD: This is a general principle, the thing made in the laboratory or a new strain selected on the basis that --

DR. MURPHY: Right. I understand the question.

DR. SCHILD: -- how much clinical evaluation do you need to prove that the efficacy and lack of transmissibility --

DR. MURPHY: Right. I think it's a very important question, and --

CHAIRPERSON FERRIERI: I will entertain expansion on this point, Brian.

DR. MURPHY: Okay. The process that's been -- that was presented in terms of demonstrating a reproducibility of a set of phenotypes over and over again, I think, builds a basis for credibility and

predictability that will serve to limit the extent of testing that needs to be done with new reassortants as they are generated using a similar approach containing similar sets of genes and genetic information.

Now what the exact number of volunteers per new reassortant would be needed to be evaluated, what that number is -- I could give you my opinion, but that will be decided by groups such as yourselves.

I think that limited numbers of studies -- if this is a virus that is planned to be used in children, adults and elderly, I think a limited safety virus replication ability in a limited number of such individuals. I think that you can get the information reliably with group sizes as small as 20.

I don't think you need to go to 100, to 1,000, to 2,000, but there will be a lot of discussion on that particular point, and I think that the information that's been provided indicates that these studies in the future can be restricted in scope.

There can't be no testing. You don't need to demonstrate efficacy or else you'll never be able to get a vaccine out in time to have it be beneficial. So it's going to be a judgment by a group such as yourself to figure out exactly how to go about making recommendations for -- and I think limited numbers.

How limited that is, I will leave that up to you.

CHAIRPERSON FERRIERI: Would you like to comment on this specific point, Dr. Kilbourne?

DR. KILBOURNE: Yes, I would.

CHAIRPERSON FERRIERI: Please.

DR. KILBOURNE: When we get into finite numbers here about how many should be tested --

CHAIRPERSON FERRIERI: Can everyone hear Dr. Kilbourne?

DR. KILBOURNE: You can't hear? Okay. That's my new hearing aid. I sound like I'm screaming. Am I?

CHAIRPERSON FERRIERI: You're doing fine. The back of the room will appreciate it.

DR. KILBOURNE: I can hear me fine. Perhaps that's all that's important.

First of all, I'd like to clarify whether Brian or others or the Committee entertain the idea that with every change in vaccine, which presumably might be as often as every year or every two years from my knowledge at this point, will there be a new clinical trial necessary?

I think Dr. Schild was driving at that point as well. I don't think there's an answer on the table about that yet. Are we sufficiently assured

about the stability of the genotype underlying the phenotype that's been presented so that we can simply add new HA and NA genes every year with the assurance that these will be attenuated viruses?

I hope we will not draw the conclusion that we don't have to do that, because I think we're talking about gene recombinatorial ratios here that are enormous. I think we already know from other studies that even the combination of HA and NA can -- which might occur with a recombinational event within the vaccinees -- can alter the replication abilities of the virus. That is, the NA actually may facilitate HA cleavage.

So there are lots of things going on here potentially. So I think this point really should be clarified early on as to whether we are starting with a premise that annual reconstruction and retrials are necessary.

CHAIRPERSON FERRIERI: Well, we haven't been challenged with that from FDA at this point, but I personally am very pleased that you brought it up, because I share the concerns about the recombinatorial events, and I would throw back to Roland whether it was his expectation that we would focus on that or not.

It's tangential but critical, but maybe not one he wanted to address today.

DR. LEVANDOWSKI: I would say I think that this issue is one that applies to whether the markers that are used for predicting attenuation apply or not. I think this is the kind of discussion that we would benefit from very greatly.

CHAIRPERSON FERRIERI: Great. Who would like to further this theme? Dr. Snider?

DR. SNIDER: Well, I think there is another aspect that we have to think about, and that is before we even get to the numbers of people -- I mean, assuming we would do some testing, and before we get to the numbers, there's the question of the types of people who would be included; because the recommendations for the high risk groups, for example, for influenza are the normal adults.

There's another issue that was raised at the last ACIP meeting about a very large group of people with what appears to be a risk factor for influenza as well as complications, and that is smokers.

So I don't know what the answers to these are, and maybe the issue could be approached more generically such as the studies that are now being

done with HIV infected and so forth. And if we come up with negative answers, we'll feel comforted, but we still are going to face the question of year in and year out with the change, of what the composition of any tested group or any clinical trial group would be.

CHAIRPERSON FERRIERI: Further thoughts on this point? Dr. Chanock, what is your opinion?

DR. CHANOCK: I'm very much of the same mind as Brian, and I agree that there is a need for testing of each product as it emerges as the vaccine of the year. But I think that there's one point that should be emphasized right up front before we get into that.

That is, there's been concern about changing -- you know, gene modifications that occur in reassortant and so forth. I think you all have to remember that the same six genes from the same pool of virus will be introduced into the reassortant each time you do it.

So those genes are fixed. They're stable, and there's no evidence from what has occurred in the past that they do undergo any significant change in the very limited amount of exposure in passage in the laboratory.

So Geoffrey is agreeing with me here, and

I feel very happy that he is, because he's a very severe and rigorous critic. So I think we could dispense with that as a problem.

The problem is the two genes that are introduced from the wild type. Ed Kilbourne has introduced the question of NA, the neuraminidase facilitating cleavage of a virus that doesn't have what is called a cleavable signature at the cleavage point.

This is a recent paper that appeared at PMA just a few months ago. If that be the case, I think that the initial studies in the laboratory which will reveal what the growth potential -- what the growth kinetics of the virus are in various types of tissue at different temperatures and in small animals and, as Peter has shown us, it may be possible to short circuit this and go right to epithelial cell cultures -- I think that as you go along, you'll be looking for and be very sensitive to any changes and any differences that might be observed.

Thus far, they haven't been observed, but I think you can -- but you have to be on a fast track, and you have to do this thing expeditiously in a timely fashion. Otherwise, you don't have a vaccine.

CHAIRPERSON FERRIERI: Dr. Schild?

DR. CHANOCK: Wait a second. Let me --

CHAIRPERSON FERRIERI: Sorry.

DR. CHANOCK: So my feeling is that limited testing by people who know what they're doing, things proceeding very quickly, lock step going from one phase to the next, I think, within a few months you'll have your answer, and you'll be able to then expand the activity, expand the use of the vaccine in larger populations. But as of now, I feel that the attenuation mutations that are built into the six genes of the donor virus produce -- when transferred into a reassortant bearing new antigens of the epidemic or pandemic strain have been -- the effects have been very reproducible and consistent and predictable.

I think it's astounding. I don't think there's any other system in the pharmaceutical industry or in vaccine development or in existing vaccines that would allow you to be so confident, of course with the proviso that the early tests might indicate that this is not the case. But up to now, I think this has been a very predictable situation.

CHAIRPERSON FERRIERI: Thank you. Dr. Schild, did you want to retort to anything there, and then we'll go back to Dr. Kilbourne.

DR. SCHILD: I don't disagree with Dr. Chanock. I just want to -- This is why I asked the question about do we know enough about the precise genetic control of virulence in terms of point mutations.

You would be able to use that information, if we had more of it, to complement limited clinical trial evaluation. There's a very good precedent for this now with polio vaccine where, because of many years of research work, we know precisely which point mutations in the genome of the polio virus Type III control virulence.

Every time a new bunch of vaccine is made, you can actually look at that population of vaccine virulence and determine the proportion of those which have the right genome at the particular position.

DR. CHANOCK: The man who did that is sitting in back of the auditorium.

DR. SCHILD: Dr. Chumakov has done some wonderful work on this, and that routinely applied.

Thinking into the future, those sort of strategies could be used for influenza, but there would be a certain amount of research work necessary to further pinpoint the precise lesions.

DR. CHANOCK: Well, I would submit that

this could be done very quickly. As Brian indicated, there are six -- I counted seven mutations in those three genes.

DR. MURPHY: It might be additional genes, though, that we don't really know about.

DR. CHANOCK: I understand, but of those that we know are major contributors, we have those -- we know the mutations in each of these proteins.

This could be tested very quickly by sequence analysis, going back to viruses recovered during the preceding 18 studies. You would have a very good idea of how stable these mutations are, not necessarily in production but at least at the distal end of the virus that is recovered from the infected vaccinees, and this could be done.

I mean, materials are in the freezer. The analysis can be performed, and I think that question can be answered.

CHAIRPERSON FERRIERI: Dr. Kilbourne, could you contribute to this?

DR. KILBOURNE: Well, everything that Dr. Chanock said before, I have no particular quarrel with, but he's defining the virus that goes into people, not the virus that may come out of people or may recombine in the field; because the acquisition

there of a fortuitously evil neuraminidase in terms of the cleavage phenomenon or other intergenetic interactions cannot be predicted.

I am very worried about categorical statements that mutations will not happen or the implication that we have stability here. We have, certainly, stability of phenotype, and I think it's been truly remarkable and, as Bob says, it might be unprecedented. But we have to be concerned about the next possibility, and that is for interaction in the field with something else. So far, it ain't happened.

CHAIRPERSON FERRIERI: Yes, please, Dr. Murphy. Don't feel neglected on this side of the room. We're composing a concerto on this side right now, even though it sounds dissonant, and I want to continue this theme. Please, Brian.

DR. MURPHY: I wanted to just clarify something that -- in my presentation. The work that I presented was done mostly with monovalent vaccines, and so the experience that I presented there has to be limited in that context.

What Ed is talking about here is a situation where you are putting in a bivalent preparation, and you're coming up with reassortants that -- None of the data that I have specifically

addresses issues related to that, and I think that information about what can come out of that needs to be considered and addressed.

I can make a very simple suggestion here of a way to address a specific concern that Ed had discussed, the possibility of interactions of glycoproteins that would lead to more cleavable phenotypes, which has been associated with virulence.

That would be very simple to do by looking at viruses that come out of volunteers or experimental mixtures of hemagglutinins for their ability to grow in the presence or absence of MDCK cells with trypsin, because that would indicate whether a more cleavable phenotype has been derived.

I would suggest that and make recommendations to people who are actively studying this that they could look at this particular property to address that one concern that Ed has brought up, which is a real concern and something that just needs to be addressed experimentally.

CHAIRPERSON FERRIERI: Dr. Cox, would you like to contribute to this?

DR. COX: Yes. I'd just like to make a couple of comments about the ease with which we can look for the presence of the particular amino acid

changes that have occurred in the viruses and monitor for what is coming out of individuals who have been infected.

As I mentioned earlier, we've actually done a lot more of that with Russian live attenuated vaccines in our own laboratory than we have with the U.S. vaccines, and it's very, very easy to devise our FLP strategies or sequencing strategies. So these things can be monitored with relative ease, if you have the person power and the sequencing power to do so.

The other thing that I would like to say is that we also attempt to keep tabs on the viruses that are circulating in nature, with particular attention to the hemagglutinin and neuraminidase genes. So we do look for particular characteristics of those genes.

Now that this recent paper has come out showing certain amino acids associated with this enhancement of cleavability of HA in the neuraminidase, we'll be looking for those kinds of changes in viruses circulating in nature.

So I think that many of the issues that have been brought up are extremely important, and we need to put in place ways of monitoring what's going

on, and we certainly can do that.

CHAIRPERSON FERRIERI: Thank you, Nancy. How does the rest of the Committee feel? Is there consensus about this direction, which is not so daunting and can be carried out? Would anyone like -- Bob Daum?

DR. DAUM: Now that the concerto has been heard, at least in its opening melody, it sounds like there's an impressive amount of data that is phenotypically driven that the attenuation mutants are rock stable, and I'm impressed by Dr. Chanock's and Dr. Murphy's comments about that.

At the same time, of course, as Dr. Cox points out, the molecular biology era sort of caught up with this whole process, and I think it's now time to get that information about what genotypic changes underlie these phenotypic changes.

It sounds also to me, listening to everybody's comments, that it would be pretty easy to do with modern techniques, as you point out. I would get it, because if something does go wrong, I don't think we'll know where to start digging in terms of where the problem might be.

So I think there's enough information that the phenotype is stable. I'm impressed by that. At

the same time, I'm mindful of the comments that I think the genotypic information gathering and the transfer experiment that was described, which sounds simple but elegant, of the one amino acid mutant that is known and produced attenuation in the recipient -- that kind of stuff needs to be done so the underpinnings will be there, and I would encourage people to high prioritize and resource that research.

CHAIRPERSON FERRIERI: Thank you. Alice Huang.

DR. HUANG: I think that the experience and the data and the exposure levels are extraordinarily impressive. For thinking about the future, we should focus very hard on one cold adapted strain and really understand that in as much depth as we can.

I think that, even thinking about sequencing, we shouldn't be daunted by that, but there are other techniques that are faster. Heteroduplex formation and single stranded nuclease will tell you if you have the change that you expected to be there and, obviously, the migration of the segments also gives you a quick read on what's going on.

I think this is tremendously reassuring, and I think that getting more of the markers, pretty

much what Dr. Daum has said, is well worth it and that we should indeed move ahead.

Obviously, we're not going to have a year or two to test these strains, but if we know the background strain that we're using, the cold adapted strain that we're using, then that really gives us some assurance of what is going on and, obviously, if we're going to have trivalent vaccines, that adds another level of complication.

I really want to congratulate the workers who have spent the time on this issue, and I think that we certainly should move ahead with it. I see a lot of advantages, and I think that the markers that we have are useful. They just need to be characterized even better, if that's possible.

CHAIRPERSON FERRIERI: Dr. Kohl.

DR. KOHL: A comment and a question.

I guess we somehow have arrived at the precedent that, with inactivated vaccines, they're not licensed as new vaccines every year, and they don't go through extensive clinical trials. In fact, I don't even know if they go through any clinical work before they're put into many of us.

It seems like there's a consensus that has evolved from the other side of the room that there

will have to be some clinical trials, at least safety. I'm astounded by the number of 20. I wouldn't take a vaccine that only 20 people were given previously. So I don't know what the right number is, but --

So that makes it a very different kind of a time frame, and especially in the situation of drift where you won't have these things in the refrigerator pretested, but where you're going to have to do it every year, I presume.

My question -- Anyway, that's the comment. The question is: Given all the work that's been done with the current ts cold adapted strain and all the other hemagglutinins and neuraminidases that have been put in it, have there ever to date been any surprises? Have there been any viruses that have grown to an unusual titer? Have there been any surprises in animal models, etcetera?

CHAIRPERSON FERRIERI: Peter Wright.

DR. WRIGHT: There are a number of us who could answer that. I think there have been no surprises in terms of increased growth or increased -- or any signs of increased virulence.

In fact, we were trying to add up the number of H1N1 and H3N2 reassortants that have, in fact , been looked at in adults or in young children,

and it's -- Let me guess, it's between 15 and 20 H3N2 and 10-15 H1N1, and the precise numbers, obviously, we could arrive at.

What has been seen and hasn't been directly commented on yet is that, when you make a multivalent/trivalent vaccine with the influenza A and B components, there have been examples where, at least to a single dose, the response to one or the other component in terms of immunogenicity has been more limited than would have been predicted from the monovalent preparation.

Interference is the term that's been used to describe it. The feeling is that, if you use the current doses of -- current amount of virus in a dose and give two doses of vaccine, that one overcomes that.

It was an issue in the first year of the large study that was commented on, and two doses were given, and then the response to all three components was acceptable, although lower to the H1N1 than it had -- than to the other two, and certainly the response to a single dose of the H1N1 was lower than anticipated.

That is an issue. I think that's a bit of an issue with the inactivated vaccine as well in terms

of a highly reproducible level of immunogenicity from year to year. It's an issue that at this point we are assuming or presuming is overcome by giving two doses of vaccine, at least on the initial exposure to this type of preparation.

I think that's reasonable, but that's an area where we have less experience, and this interference has been a phenomenon that's been seen more than once, and is not entirely predictable in terms of either the strain or, certainly, the reason for it.

CHAIRPERSON FERRIERI: I don't wish to ignore you, Diane. If we could just have a response here from Brian.

DR. MURPHY: A quick response and a surprise was, when we gave doses that were significantly higher than 10^7, seven, five, eight logs, we saw reactions in individuals that were typical of influenza reactions where we saw some febrile responses, some headaches.

So I think that, based on that experience and, when you go back in the literature, you can see similar types of reactions described with the okuda strain and other viruses that have been given and they were given at high doses, and this is one of the

reasons -- one of the thinking that leads to the limit of 10^7 as an acceptable dose of this particular virus vaccine.

CHAIRPERSON FERRIERI: Dr. Finkelstein.

DR. FINKELSTEIN: I just want to make a comment about the n of 20 as well. I wasn't -- It wasn't clear to me what kind of a safety study you could do with a n of 20, because you're not going to pick up any kind of untoward events that happen less than about 20 percent of the time or some very large number, and you would not be able to get sort of the profile that we get with the very large studies that we do, and you would not be able to pick up the more -- less common -- more rare but very worrisome complications.

DR. MURPHY: Again, you have to think of this not in terms of a single product but in terms of a process, and that every single unit that comes out on a yearly basis has a history of similar such preparations.

So every single unit that gets produced on an annual basis does not have to go through the extensive testing that you do. Like, for example, the inactivated vaccines that are currently licensed right now do not go through huge trials of efficacy, safety,

etcetera. I don't even actually know if they go through any trials. Do they? Are they limited?

DR. COX: No.

DR. MURPHY: So I think that, when I talk about an n of 20 -- and don't -- That's a thought of somebody on this side of the table, and you don't -- I've -- We've done a lot of studies in humans with these viruses, and what you would learn from 20 children who are seronegative to a virus tells you is absolutely predictive of whether -- Strange as this might seem, and I know there are a lot of skeptics, but we can identify viruses that are unacceptable for further evaluation when they're given to seronegative humans in small numbers.

The n of 20 -- you guys can decide that, and FDA will figure out what they want. Don't take that, but this is the point that I think is important. Small numbers, intensively studied in the context of a vast experience with tens of thousands of individuals tested before, give us lots of reassurance.

DR. FINKELSTEIN: I would understand that if you felt that we had the experience that you're talking about that this model was well tested of altering it from year to year, which is what I think

is the case right now for the current vaccine which is used. But it would seem to me that it might be valuable to get a couple of years of good -- you know, randomized clinical trial experience to really feel a sense of confidence that the model works before you go into the second stage of just doing it on 20 people and using your experience.

CHAIRPERSON FERRIERI: Dr. Levandowski?

DR. LEVANDOWSKI: Yes. I would just like to bring up something else along the lines of attenuation. We've been talking mostly about the two ends, the genetic or attenuation markers, and then clinical trials. But maybe there's a middle ground.

If it's possible, I'd like to hear maybe some additional comments from those who know about attenuation and animal models. Brian Murphy and Dr. Kilbourne and Dr. Schild maybe might have some thoughts about that, or others.

CHAIRPERSON FERRIERI: Okay. Let's pursue that for a little bit. Who would like to start on that? Dr. Murphy.

DR. MURPHY: The vaccines that have been made up and tested to date have been evaluated in ferrets as a part of their routine evaluation. Ferrets are one of the only animals that get sick with

wild type influenza viruses. They sneeze, and they're not really happy, although I've never seen one actually sick.

The ferret data has been totally compatible with the cold adapted phenotype, ts phenotype and 6/2. If they have those sets of properties, they're attenuated in ferrets.

That is a reproducible phenotype. It can be used -- I wouldn't -- I mean, I would be happier doing limited numbers of studies in humans and putting them back into ferrets.

CHAIRPERSON FERRIERI: One hundred ferrets, Brian?

DR. MURPHY: I don't think we need to do that many ferrets. You know, maybe 20 would be a good number.

CHAIRPERSON FERRIERI: Let us get back to the point. Dr. Schild, would you like to add to this discussion, this specific point?

DR. SCHILD: We have a number of animal models. None of them are ideal, but we should make the best value of what resources we have in that respect. I think they do have valuable potential as pre-clinical models for attenuation.

CHAIRPERSON FERRIERI: Thank you.

DR. SCHILD: Perhaps there should be additional work on identifying better animal models.

CHAIRPERSON FERRIERI: Dr. Kilbourne, do you have a comment on this?

DR. KILBOURNE: Well, I'll take the opportunity not to comment, but simply to insert a plea that we not make comparisons between the amount of testing that has been done for inactivated vaccines versus a replicating agent, which is a new ballgame, the first vaccine ever introduced into the human respiratory tract where it has all the potentials for replication, recombination, etcetera.

I think the issues are quite different in the two categories.

CHAIRPERSON FERRIERI: Dr. Webster, do you have an opinion on this specific point?

DR. WEBSTER: Well, we were talking about animal models, and I don't think you can do better than the ferret model. That's what we have to work with initially.

CHAIRPERSON FERRIERI: Roland, is that carried as far as you would like? I think we -- Go ahead.

DR. LEVANDOWSKI: Well, I might ask further if -- Let's take the ferret model. What are

the, I guess, maybe the detrimental aspects of that model or are there parts of that model that would not reflect what we would want to know in terms of attenuation of an influenza virus?

There are ways to determine, and there have been criteria that have been set up, to look at infection of ferrets, looking at their illness, monitoring temperature, looking at virus in the upper airway and the lower airway.

My understanding previously was that there was some correlation between attenuation and what happens in the ferret, but are there aspects that are unpredictable in the ferret model?

CHAIRPERSON FERRIERI: Dr. Murphy again.

DR. MURPHY: I say this with the admission that I've never given an influenza virus to ferrets. It's always been done by John Massab as part of these studies. But the ferrets have a different body temperature than humans. They're 40 degrees, 39-40 degrees.

So it's going to be very difficult to characterize exactly the level of effect of temperature on replication of the virus in an animal whose body temperature does not mimic that of humans.

I'll just say parenthetically, we've given

these viruses to chimpanzees, and chimpanzees are not a good model for -- who have the same body temperature as us. They're not a good model for influenza. Ferrets are the best we have, really.

CHAIRPERSON FERRIERI: We have audience participation. Could you give your name and group?

DR. MONTO: Arnold Monto, University of Michigan. We have extensive experience, as you might guess, with the ferret model and the live attenuated vaccines.

The question was raised about surprises, and have there been any surprises. Yes, there have been surprises back in the Seventies before the ability to identify the 6/2 constellation was available. Those viruses -- and there's a paper I have in front of me -- I'm sorry I don't have a transparency -- which showed that five of these without the 6/2 constellation were, in fact, underattenuated in humans and also showed underattenuation in ferrets.

So there is, based on this blind experiment when we didn't know what we were dealing with, a very good correlation between the ferret model and humans.

I might add parenthetically that I don't

think you're going to get answers to the issue of interference, if that is what is going on, in terms of immunogenicity, and I think that has to be kept as a separate issue. But in terms of the safety, you're not going to be able to do very much better than we have been able to demonstrate in the past with the ferret.

CHAIRPERSON FERRIERI: Dr. Poland.

DR. POLAND: I'm sorry to interrupt. Dr. Monto, before you leave, I wonder if you could just tell us the reference to that paper.

DR. MONTO: Journal of Infectious Diseases, December 1982, page 780. The authors are Massab, Kendall, Abrams, and Monto.

CHAIRPERSON FERRIERI: Thank you very much. Dr. Snider, we'll keep this brief, and then we'll be moving on to the second point -- second question.

DR. SNIDER: Well, I just wanted to reemphasizes again that, when this Committee and FDA have to address issues down the line in terms of who the vaccine would be indicated for and, given what we know about the epidemiology of influenza and given what few papers -- admittedly, few papers I have read about the study subjects, there's not a good match in

terms of those who would be at high risk, having been in the trials.

I'm not suggesting that we have to do that every year in order to prove the point, but somewhere in the repertoire of a trivalent vaccine, it seems to me, there ought to be a study looking at all of those populations that we would put a high priority on vaccinating and not just normal subjects.

CHAIRPERSON FERRIERI: Thank you very much. I'm sure they'll put that under advisement.

I won't attempt to summarize everything we have said. It will be in the public record. You've heard considerable discussion on the issue, ranging from the phenotypic characterization to the enthusiasm for the genomic characterization and changes that conceivably could occur, as well as some discussion of the studying on a year to year basis what transpires.

The second question is to comment on the biological containment for the development and manufacture of life attenuated influenza virus vaccines.

You heard discussion of this in terms of the laboratory containment, and I would like to hear your reactions, the Committee as well as the consultants' thinking on this.

Dr. Edwards?

DR. EDWARDS: I wondered if Roland could comment a little bit about the safety containment for the generation of the inactivated vaccines that exist, and has there been any studies of people who work in those plants and some evidence of communicability that currently exists with the current strains?

DR. LEVANDOWSKI: Well, I'll try to answer that, but it's going to be very vague at best. As you know, the strains are changed almost every year, and the manufacturing facilities seem to continue.

I don't know what the absentee rates are at the plants during the manufacturing season for influenza virus vaccines, but the old saw is that everybody who works with influenza doesn't get influenza, and somehow there's this notion that there's a subliminal exposure to the viruses as they're being handled in the eggs, and that may be, I guess, a form of the live virus vaccine.

There are not -- The measures that are taken in the production facilities, as I mentioned at the outset, really are to protect the product. They're to protect the material coming out of the egg, the allantoic fluid harvest, and not really so much to protect the workers.

I don't know whether there is anybody from manufacturing who would like to comment, but really, except for being able to immunize the workers with current vaccines, I don't believe that there are any other measures that are used routinely. I think that all manufacturers do offer that but, of course, if they're working with a new strain, it may be that it's, you know, not quite the match of the vaccine you would like to have.

CHAIRPERSON FERRIERI: Dr. Murphy, you had addressed this point, I believe, in your presentation. Do you have anything further to say?

DR. MURPHY: No. No, it's a BL-2 agent. It's been given to humans at doses of 10^7. It grows to 10^8 in the eggs. That's the information we have to work with. Highly attenuated in humans, won't -- doesn't transmit.

CHAIRPERSON FERRIERI: Dr. Eickhoff, and I apologize for not recognizing you at the end of the previous discussion.

DR. EICKHOFF: No problem. I think the lack of containment -- or containment should not an issue when -- even with what we all recognize as human pathogens. But I know when H5N1 came along, there certainly were containment issues.

I wonder if Dr. Levandowski would like to address those, or Dr. Webster.

CHAIRPERSON FERRIERI: Dr. Webster, why don't you start?

DR. WEBSTER: It goes almost without saying that under these circumstances containment facilities would have to be used. For the introduction of a new subtype for the production of inactivated or attenuated vaccines, those things would have to be taken into account.

We have to keep in mind that's a very good question about the production of an inactivated vaccine. These, until they're inactivated, are live and non-attenuated. So it applies to both kinds of vaccines.

CHAIRPERSON FERRIERI: Did you wish to say anything further, Roland, before we move on?

DR. LEVANDOWSKI: No, except that I think it is a very thorny issue. There may be great differences between strains that are currently circulating in people. The H1N1 and H3N2 type strains considerations could be considerably different, as they might have been for a brand new subtype.

CHAIRPERSON FERRIERI: Dr. Greenberg?

DR. GREENBERG: I was -- My question was

similar, the containment issue. I assume Roland is concerned about it for brand new hemagglutinins and not for the year-to-year drift. Is that correct, that you were asking advice about what would happen like in 1997?

DR. LEVANDOWSKI: Well, the question is a little bit nebulous, isn't it, but it's meant to be open. So that if there were concerns in either direction that would be entertained or should be entertained, we would certainly like to hear those comments from you.

DR. GREENBERG: The only other point I have is that the master donor cold adaptive strain is an H2 strain which has not circulated since 1968. It's obviously been worked with since that time, and there is a fair -- So that virus represents an example of introducing a hemagglutinin that is not around, and that hasn't spread.

So that gives me a fairly good feeling that this is not a dangerous situation.

CHAIRPERSON FERRIERI: Would anyone -- I think that we have consensus on this. Would anyone like to speak contrarily to this point? And we can accommodate the vagueness. That's fine.

Yes, Dr. Breiman?

DR. BREIMAN: Thanks. I was actually just going to ask Dr. Webster for a clarification. Do you mean that containment would have to be followed in the research setting or within production facilities, in which case, if it's within production facilities, even if we're talking about the current approach, inactivated approach, I don't think that most manufacturing settings are geared to do that.

So I don't know what kind of steps would have to be taken and how that also would slow down the process that we talked about before.

DR. LEVANDOWSKI: Could I just qualify something that I said earlier about the production facilities. I don't mean that there are no measures in place for protection of the workers. Of course, most of the critical processes occur under conditions of laminar flow and controlled air flow, and there's a lot of very careful planning that goes into building the facilities to do that.

I don't mean to suggest by my comments -- they were a little bit flippant perhaps. I don't mean to say that there's nothing done in current manufacturing facilities that keeps -- serves as a barrier between the workers and the product.

CHAIRPERSON FERRIERI: Yes, and barrier

clothing is used as well. Any further comment on that? Dr. Webster?

DR. WEBSTER: We would be concerned -- It would depend on the subtype that we were thinking about. If it was an H5 or an H7 that is highly pathogenic in chickens, in the eggs, that could destroy the eggs where the vaccine is being produced, then it would be a problem. We would have to decide this ahead of time.

Under normal circumstances, it would not be a problem.

CHAIRPERSON FERRIERI: Thank you. With your permission then, Committee members, we'll move on to question 3 on the screen. Please comment on the introduction -- and we touched on this theme throughout the past several minutes -- the introduction of new influenza virus strains and subtypes into the community in the form of live attenuated influenza virus vaccines.

At various points we've indicated that the risk appears to be very minimal, but I would entertain more in depth discussion of this point.

Dr. Hall, thank you.

DR. HALL: Pertinent to this, I think, is the yearly posed clinical studies that people seem --

there's consensus that would need to be done with a new -- with the new yearly reassortant virus.

What I'd like to ask is what would be the real goals of these clinical trials with each new vaccine, assuming that we had to do that, whether it's 20 or 100 or whatever else; because, certainly, within that you could tell whether it's safe, whether it's, you know, genetically stable even and its immunogenicity.

I'm very encouraged by the techniques that have been suggested here of determining whether there is a change or whether the pathogenicity, and how closely that correlates will still have to come. But that's apt to occur, I would think, at a very low level.

So that doing 20 or 100 or whatever else is probably not going to determine that. That still doesn't abrogate, I think, the concern that what is going to happen in the subsequent epidemic or period of activity.

You would have to have so many people immunized in the circulation of the wild virus that it's only after years that you could tell whether this is going to be truly a problem, because it's probably going to occur at a very low rate.

So I think we'd have to sort of differentiate that the purpose of a yearly clinical trial would be quite different than trying to say that this is not going to be a problem in terms of reassortant virus or in the subsequent years, and that would be maybe years until we will know that.

CHAIRPERSON FERRIERI: Don't you think that the response in the study should be adjusted to what is happening in the community, and the epidemiology of what might be circulating and any surprises would drive the engine in terms of what is done and the intensity of this?

Dr. Hardegree?

DR. HARDEGREE: In terms of the reassortants, some people have suggested that there might be mathematical models that could be introduced. We heard Dr. Wright talk about a rule that people may be looking at polio transmission.

Are there any models that anyone knows that have been applied to this or that could be applied to anything to deal with the potential for reassortants?

CHAIRPERSON FERRIERI: Thanks, Carolyn. Anyone in the audience would like -- please, and give your name and where you're from.

DR. WHITAKER-DOWLING: My name is Pat Whitaker-Dowling. I'm from the University of Pittsburgh.

I have done some studies that are unpublished looking at mixed infections of wild type virus and the cold adapted vaccine. What I find is there's a very strong selection in cell culture for reassortants that contain the m gene of the vaccine, which we found in cell culture experiments and in animals is a dominant gene.

We did a small human trial, as Dr. Wright referred to, and we saw the same kinds of reassortants coming out in the humans.

CHAIRPERSON FERRIERI: Thank you very much. In response then to Dr. Hall's question and Dr. Hardegree's, do we have any other answers from the panel here on my left? I see you, but I'm looking at this side of the room right now. Dr. Wright?

DR. WRIGHT: Well, I --

CHAIRPERSON FERRIERI: Don't quote Dr. Edwards' work, though. We'll let her do it.

DR. WRIGHT: No, I don't -- I don't know that what I say is going to be very profound, except that I think that this is a fairly promiscuous virus that in birds and animals, in man is exploring

opportunities for reassortment all the time, and that I doubt we're going to contribute substantially to that effort on the part of influenza virus by what we do with cold adapted vaccines.

CHAIRPERSON FERRIERI: Dr. Edwards?

DR. EDWARDS: Actually, I just wanted to see what your thoughts were for what that meant, the predominant.

DR. WHITAKER-DOWLING: Well, I don't know whether Dr. Murphy would agree with me, but there is some evidence that the m gene confers some attenuation, too, from Dr. Murphy's own work. He found, initially using a Korea wild type background, that the m gene conferred attenuation.

We certainly find in cell culture that it does confer reduced growth capacity, that m gene. So we think that, actually, if this reassortant predominance occurs in the human population, as we have indication that it will, that you're actually going to be generating attenuated viruses, preferentially.

CHAIRPERSON FERRIERI: Yes, Dr. Kilbourne, and then Dr. Snider.

DR. KILBOURNE: Well, I have to register my ever exception here. I mean, we should be reminded

that you would take two viruses of equal pathogenicity and make one which is more virulent or you can take a virulent one and an attenuated one, and most of the time you tend to lessen the virulence when you do that, for statistical reasons and the gene reshuffling.

It's been shown experimentally by Rott and Schultacek some years ago, it's been shown in our laboratory that you do not necessarily arrive at a reassortant of intermediate virulence. In other words, I think a scenario that, if your ca virus escapes into the community, it's just going to make the wild type a nicer virus doesn't necessarily follow.

I think that should be kept in mind, because we have to consider all possibilities in terms of future litigation and so forth when this is released.

CHAIRPERSON FERRIERI: Dr. Snider.

DR. SNIDER: Well, Dr. Hall posed a question that I don't think got completely answered, and I would like the answer to it, too, in terms of that we are going to do the clinical study, at least at the beginning on an annual basis, what are we going to look for?

I was under the impression that we were primarily looking to see that the virus indeed remained attenuated in terms of its replication and that excretion was the same as had been experienced in previous studies.

Prior to that, of course, people had suggested that we would look at the genotype and make sure that that had remained stable, as everyone expects it to do so. Then it seems to me that one would ask the question about whether we wanted to look at not rare but the common adverse reactions and ensure that they were in the same ballpark as one would expect, based on previous experience.

That's about all, it seemed to me, that you could get out of any small study that would be feasible to do, but if there's other things, I'd like to know -- that we ought to be looking for, I'd like to know what they are.

CHAIRPERSON FERRIERI: Dr. Wright?

DR. WRIGHT: It's not here before you, and in some ways it wasn't the topic of this particular meeting. But I would respectfully submit that most of the past 20 years we have done that experiment, either on small or large scale.

So I am hesitant to think that we will

learn anything from small trials at this point with the currently circulating H3N2, H1N1, nb viruses. What you can learn from a small trial, I think you've summarized.

We do build on what we know. We can look very precisely at the amount of shedding of each of the strains, if we give a trivalent vaccine, but obviously, we can't identify untoward effects.

The experience with these vaccines -- I know it's not entirely satisfying to an epidemiologist -- is that, in fact, we have -- Almost everything that we wanted to know about this virus, we probably knew after the first -- in some ways the first several years of testing in terms of the safety pattern and the replicative pattern and so forth.

One would think that, as one got to larger numbers, one would see an expansion and rarer events would emerge, but so far that has not been the case with this or, I would submit, with rotavirus vaccine or a number of other live vaccines that have been looked at.

You really can discriminate a lot on the basis of small numbers of carefully studied individuals.

CHAIRPERSON FERRIERI: Frequently, not

satisfied the statisticians either. Dr. Finkelstein?

DR. FINKELSTEIN: I would just say that it might be useful to actually put some thought into what trials you would design and what you would want to be looking for, both for the more common profile of side effects that maybe aren't that clear at this point, since you're giving it in kind of a new fashion.

Also, I think it would probably be useful to urge a surveillance that would be in place afterwards as well, and to sort of put some thought into the design of the surveillance, what you're going to be looking for, considering this is all a new approach.

CHAIRPERSON FERRIERI: Dr. Greenberg, and then Dr. Poland.

DR. GREENBERG: I was struck by the idea of mathematics. Do you have any idea of about how many -- This seems like perhaps a strange question, but how many new genes are -- How much more genes of influenza would you be adding to the United States if you vaccinated everybody? Is it a drop in the bucket or would there be a substantial --

So if each child gets 10^7 doses, every child in the United States, would you be adding a lot of new influenza genetic information to the burden

that year or does each child actually have 10^9. So, in fact, you're only adding 1/100th more genetic information?

I'm just trying to get a feeling of how much you're going to change what's going on out there, if you really had a vaccine going on each year.

CHAIRPERSON FERRIERI: Dr. Murphy?

DR. MURPHY: Everybody gets infected with these influenza viruses, wild type viruses. The wild type viruses grow one-thousandfold more efficiently than the attenuated viruses.

Not every kid gets infected every year with a wild type virus, but the magnitude of total number of viruses that exist out there will actually likely go down if a virus that grows one-thousandfold less well is used and it prevents an infection or modifies an infection that occurs at almost 100 percent frequency.

CHAIRPERSON FERRIERI: Dr. Poland.

DR. POLAND: I was going to mention the same idea that Diane did, and I think is maybe worthy of discussing a little broader.

That is, we have a very good surveillance system for picking up new, if you will, natural reassortants, and it seems to me logical that, as long

as there is biologic plausibility for some degree of possible harm from these, that that same surveillance system could be, if you will, additionally tooled to provide surveillance for any unexpected surprises for these reassortants.

The second thing that I wanted to ask is a point of information. Is there any evidence that either kind of these natural reassortants or manmade reassortants -- that the genetics of that have been such that there's -- it has ever conferred antiviral resistance, for example, to amantadine or ramantadine, and do we understand the genetics of that resistance so that -- Please, inform me.

CHAIRPERSON FERRIERI: Dr. Cox?

DR. COX: Yes. We do understand the genetics of resistance to amantadine and ramantadine very well, and these viruses do not have the mutations that confer resistance. So that sort of answers that question.

I did also want to make a comment in response to the issue of doing surveillance for possible reassortants. I had mentioned a couple of times previously that we had actually done quite a lot of work with the Russian cold adapted viruses.

One of the reasons that we got interested

in this initially is that we understood that the live attenuated Russian vaccines were being used rather widely in their populations, and we were very interested to see if the introduction of these viruses into the Russian population would have an effect on the circulation of cold adapted genes and reassortment and so on.

So we actually were looking at -- During our surveillance, we were looking at the internal genes as well as the hemagglutinin and neuraminidase genes in viruses isolated from Russia. We actually saw -- We had rather limited numbers of viruses, admittedly, but we didn't see any evidence that these internal genes of the live attenuated vaccines were being reassorted and then transmitted in the strains that were circulating.

CHAIRPERSON FERRIERI: Any further comments on this specific question we're addressing? Dr. Kohl?

DR. KOHL: I'm concerned about the worst case scenario, and the worst case scenario, to me, is we get our H7 strain that we're worried about and we put it into a reassortant, and we give it to a minority of the population, which is what happens in this country when we immunize against influenza, but

millions of people, although it's still a minority of the population.

We then get a new recombinant between a circulating, already wild vaccine and this H7, which gives us a virulent H7 recombinant that we now have basically introduced and is circulating in a partially immunized population.

We have created then our own epidemic. To me, that's the worst case scenario. What's the response? Is that -- How likely is that? Can it ever happen?

CHAIRPERSON FERRIERI: Well, Robin Cook may have the answer. Who would like to seriously address this? Dr. Webster?

DR. WEBSTER: The worst case scenario is the worst case scenario. The likelihood, in my opinion, is very, very small. I mean, if we're going to have an H7 put into this vaccine, we're going to put one in that has -- doesn't have the basic amino acids in the hemagglutinin.

We're going to have the six segments from the attenuated virus, and the possibility of producing the monster strain -- you can't completely rule it out, but the likelihood, in my experience of having made very many of these reassortants, is very unusual

to make something that would be this monster strain.

CHAIRPERSON FERRIERI: Dr. Hall?

DR. HALL: I just wanted to have Nancy, if she would, clarify the part about the resistance to ramantadine or amantadine in the reassortants, in that are you saying that if, say, somebody who received the vaccine was already on ramantadine or being treated with ramantadine or amantadine, that under the pressure of that, that the virus would not be able to become resistant?

DR. COX: No, no. I wasn't implying that. I was saying that the virus -- the cold reassortants are not themselves resistant.

DR. HALL: Right.

DR. COX: Of course, it is possible that an individual who was on amantadine or ramantadine would generate resistant strains while on these drugs. That's true if they get wild type virus or anything else.

DR. HALL: Has that been looked at within the in vitro at all, whether these viruses are, when subjected to ramantadine or amantadine? Certainly, that could happen in the high risk patient, that you may actually end up with both of those, the vaccine and ramantadine or amantadine.

DR. COX: I don't know if it's been done in vitro. I don't know if anyone has done those particular studies, but certainly, it would be a similar situation, although the transmissibility would be different, but we do have the situation in nursing homes all the time where wild virus is introduced into a vaccine or partially vaccinated population.

The population is put on ramantadine or amantadine prophylactically, and some people are treated. Resistant virus can arise, and then subsequently be spread.

The potential for spread of these viruses is just much lower than the potential for spread of a wild type virus.

CHAIRPERSON FERRIERI: Do you wish to add to that, Dr. Murphy?

DR. MURPHY: I'd like to respond to Dr. Kohl's question, if I may. Is there something else to be said about this?

CHAIRPERSON FERRIERI: Use the microphone before you address Kohl's question. Dr. Snider, did you want to address this issue of in vitro studies? Do you know of any that have been done? Is that what your hand was up for?

DR. SNIDER: It's about the issue that

Nancy was speaking to.

CHAIRPERSON FERRIERI: Yes, please go ahead.

DR. SNIDER: And my question was -- It just occurred to me -- do we screen the strains that we use for vaccines each year for resistance? It seems to me, we probably don't, because it's irrelevant for inactivated; but maybe we do.

If we don't, it certainly would seem that, for live attenuated, you would want to do that.

CHAIRPERSON FERRIERI: Nancy -- Dr. Cox?

DR. COX: We actually screen all the viruses -- all the foreign viruses that we get for any resistance, and a goodly proportion of the U.S. viruses, but normally we don't do that screening until after vaccine strain selection has already taken place. So we don't do it in advance.

CHAIRPERSON FERRIERI: Thank you. Now Dr. Murphy is going to expand on the monster strain of Dr. Kohl.

DR. MURPHY: Right. I think that, if we get into the situation that Dr. Kohl describes, we'll be lucky. This is an unusual comment probably. You're wondering what is this person talking about, but it's this.

The implication in that is that we've been able to generate a live attenuated virus vaccine fast enough, deliver it to a large percentage of the population in the U.S., before the virus comes to the United States. Okay? And that knowing, you know, the epidemiology and the transmission of the wild type viruses, if this appears in February, you know, the chances of us manufacturing, etcetera, being able to develop a large number of doses to give to the human population -- if we're lucky, we'll get it done by August or July or something of that -- You know, we'll be extremely lucky.

So let's say we introduce it at that point in time. Okay? It's unlikely that the wild type virus is circulating in our population at that time, because they're not going to -- The other viruses are -- The wild type virus is not generally epidemic then, but let's say they are, and let's say we do generate a reassortant, as the one that you described.

What's happening, though, is that at the same time that particular reassortant is being generated in extremely low numbers, this wild type virus is invading us from on both coasts, coming in on airlines, on Boeing jets, etcetera, and is seeding the United States population in multiple different

locations.

So as I say, I think that if we get the virus and distribute it fast enough to be in the situation that you are describing, I would say that we would be doing our job as public health sort of individuals, and I would actually be extremely pleased that, if we could even be in this situation of being able to look at that scenario.

I think our past experience has been the vaccines have always been introduced after the virus has gotten into the population.

CHAIRPERSON FERRIERI: Dr. Breiman.

DR. BREIMAN: It's interesting that the real doomsday scenario may be our inability to respond to a pandemic rather than these other issues.

DR. MURPHY: Absolutely.

CHAIRPERSON FERRIERI: Yes.

DR. BREIMAN: But I think -- I mean, I just want to go back to one basic question for my own understanding, again of something that Dr. Webster said, that all important basic amino acid segment from HA genes that presumably be removed.

Is there a potential that through some sort of recombinational event, that they could be reinserted and then become again, you know, virulent

from that standpoint?

Then, as Dr. Kilbourne had suggested earlier, we can't always assume that the ultimate combination that results from a natural reassortant might be intermediate. I mean I suppose that one could imagine a Kohl -- we'll have to call it a Kohl bug, I guess, could arise from that, that would in fact be very transmittable and potentially lethal. But I think not, without that basic amino acid segment.

CHAIRPERSON FERRIERI: Dr. Kilbourne.

DR. WEBSTER: I'm going to -- Oh, sorry. Did you want me to respond?

CHAIRPERSON FERRIERI: I'm sorry. It was Dr. Webster you were addressing it to?

DR. BREIMAN: Well, you brought it up, but maybe Dr. Kilbourne is the right one to respond. I don't know.

CHAIRPERSON FERRIERI: Well, I'd be happy to have both of you respond. Let's have Dr. Kilbourne go first, and then we'll get back to you, Dr. Webster, and please use the microphone.

DR. KILBOURNE: The point I wanted to make had to do with the --

CHAIRPERSON FERRIERI: Louder, please, Dr.

Kilbourne.

DR. KILBOURNE: A rather facile assumption is that -- is a standard scenario for pandemic introduction. We've had four instances of potential pandemic introduction, and the scenarios have been duplicated only twice, in '57 and '68. That is, something comes in. It spreads rapidly, encompasses the globe within a year.

In 1976 we had a virus introduced at Ft. Dix. It went from person to person through at least seven generations. It went nowhere after that. In 1997, as we all know, we've had a zoonotic introduction in Hong Kong which went no place.

So we have different scripts that may be followed by the virus, and it's not simplistically that the virus will emerge. If it's a new subtype, away we go.

So I think that's important and relevant to the question Dr. Kohl and Dr. Murphy were discussing. That's the only point I wanted to make here.

CHAIRPERSON FERRIERI: Fine. Dr. Webster?

DR. WEBSTER: First, to return to Dr. Kilbourne. There are many more introductions of avian and animal viruses into human populations than we ever

realized. Most times, these are dead ends, and the number of times they go on is extremely limited.

To answer the question about the connecting peptide, the basic amino acids in the hemagglutinin and the possibility of repair in the human population, I'd like to turn that one over to Dr. Cox, because some of their people have done -- made the appropriate reverse genetic virus to preclude this happening.

CHAIRPERSON FERRIERI: Dr. Cox, and we'll be wrapping up this particular question very soon.

DR. COX: Okay. When we -- It was obvious that we needed at least to make experimental vaccines to the H5 virus and, of course, this Committee had made a very strong recommendation that experimental vaccine, H5 vaccines, be made.

We very carefully looked at the basic amino acid cleavage site, and it's reasonable trivial to remove it; but the possibility that it would be reinserted after replication in eggs or in humans was considered.

So we made some additional alterations, based on a study that had been done by Mike Purdue and his colleagues which suggested a mechanism for insertion of the multiple basic amino acids. So we

altered some additional nucleotides that would make it less likely for the secondary structure to form that was postulated to make it possible for this insertion to take place.

It doesn't mean that it couldn't happen, but what we also did was to make sure that there would be studies in chickens and studies done in ferrets and so on and so forth. So there would be a lot of intermediate safety steps before the virus would ever be used outside of strict biocontainment facilities and so on.

So I think, although it's rather laborious, we've learned a great deal. We've really taken a lot of these things into consideration in the sort of dress rehearsal that we've had, and we certainly don't have all the answers, but we know a lot more about the steps we would have to take if we ever have to deal with one of these highly pathogenic avian strains again.

CHAIRPERSON FERRIERI: Thank you. I think where we are is that we take seriously the possibility that an undesirable strain could emerge, but based on all of the data available, we've been reassured by our experts that this is most unlikely and that we would be prepared to deal with it, if something should

occur.

Let us move on then to the last question that Dr. Levandowski is posing for us: Please comment on possible clinical consequences of live attenuated influenza virus vaccines, including secondary bacterial infections and hypersensitivity reactions.

So I'd like the Committee and guests to comment on very obvious possible secondary infections, pneumonia, sinusitis, otitis media, and then any of the allergic reactions, including acute hypersensitivity reactions Type I, that could occur.

We've heard considerable information from Dr. Wright's presentation that should help us. Dr. Hall?

DR. HALL: I think, from the evidence given and data that we do have, that it's clear that these would reduce the bacterial complications that occur, as we've mentioned earlier. Most of those, I think, would be, obviously, in the upper respiratory tract.

I think it's impressive that in the studies even from Hayden -- I guess it's actually Walker who did the studies looking at the effect of otitis or middle ear pressures again -- this is the tool they were using, because it was adults and

experimental influenza.

Granted that that does not equate to otitis media, but there's a pretty good incidence -- that in their group -- This was a study for an anti-neuraminidase trial, but in the placebo group, 73 percent, I think it was, had abnormalities in middle ear pressures as adults, and that there are data that also Peter has shown that actually in children otitis media is reduced with the vaccine.

So I think all of those would be very reassuring.

CHAIRPERSON FERRIERI: Other comments from our clinicians, pediatricians? Dr. Kim, and then Dr. Daum.

DR. KIM: I guess a question is that are there any specific features of influenza virus that contributes to these kind of complications, compared to, let's say, other respiratory viruses?

For example, looking to data published in RSV, a story appears to be similar that, if you decrease the RSV infection, then secondary bacteria infections which is otitis media can be noticeably reduced.

My question is that are there any specific features of this virus that makes them different from

other respiratory viruses?

CHAIRPERSON FERRIERI: Dr. Wright, and then perhaps Dr. Murphy.

DR. WRIGHT: I think, although I'm not sure that I have absolute proof -- certainly, there's a lot of data to suggest that influenza in some way more than other viruses leads to de-epithelialization and loss of ciliary activity in the respiratory tract.

That is assumed to predispose to secondary bacterial infection, both by interrupting this sort of escalator that carries mucous and pathogen out of the lower respiratory tract and out of the middle ear and also through just allowing invasive events to occur.

I don't think it's exclusive to influenza, but I think it's more a characteristic of influenza. It certainly seems to be in these primary epithelial cells that we're looking at when compared to RSV, for example, which we've looked at.

I think that that is what -- that is thought to be the mechanism, and one nice example is perhaps in the chinchilla model that Scott Gebink has worked on where he tries to get a pneumococcal otitis. Using pneumococci alone, he has to directly inject the pneumococci through the tympanic membrane, and then it will establish a middle ear infection.

If you first infect with influenza, we demonstrated that you could then simply put the pneumococci into the nasopharynx, and you would get pneumococcal otitis, and that this pneumococcal otitis could be prevented either with a pneumococcal vaccine or with an influenza vaccine.

It doesn't get quite at why it's different than the other viruses, but that it does this, I think, is almost inescapable.

CHAIRPERSON FERRIERI: Dr. Murphy, would you like to add to this?

DR. MURPHY: Just a -- The bad thing about influenza compared to RSV, which is actually a more severe infection, is that influenza changes its hemagglutinin. So it keeps on having more and more opportunities to do the same thing, which it does very well.

So that where you might have one or two severe RSV infections, you'll have more than that with the influenza viruses. So that's what differentiates influenza viruses.

The other point is that influenza virus grows unbelievable well in the respiratory tract of humans. We've calculated -- We've measured yields of virus up to the levels of 10^7 per ml. of wash, which

means that this virus is growing to 10^8 infectious units in the respiratory tract epithelium.

This is a tremendous level of viruses. In the pathological studies they have done, Peter talks about epithelial desquamation. Back in 1957, they did a -- Molder and Herse did an unbelievable study where they looked at pathology in the respiratory tract of humans infected with the H2N2 virus, and it completely desquamates the epithelial cells.

CHAIRPERSON FERRIERI: Let me refocus the discussion and the point number 4 from FDA. We have seen data presented by Dr. Wright comparing vaccinees who received the live cold adapted vaccine, lots of children, comparing them with placebos and looking at endpoints such as otitis media and other possible adverse events.

Have you seen anything that would lead you to believe that we should have more concerns? What is your interpretation of the extant data?

Dr. Daum, and then we'll get back to Dr. Kilbourne, I believe.

DR. DAUM: I'd like to hear some more discussion about this beyond what I have to say as well. But there's certainly a consensus of data, mostly in the stuff that Peter presented, that the

likelihood of the vaccine virus being associated with bacterial infection seems low.

On the other hand, it also seems like, if this was the sense of all of the available data, that we could use some more. The H-flu story -- for example, the animal work that you presented -- I mean, there's clearly a tremendous difference in the bacteremia rate with the wild type and the vaccine virus strains, but there was still some bacteremia in the animals that got the cold adapted vaccine.

There are now better animal models of pneumococcal disease than there were, and these could perhaps be exploited to look at some of these issues, at least in vitro, as well.

I think it's unlikely that there's going to be a problem here, but I would like to hear some more discussion and think perhaps about how we would approach this as a medical community to ensure that this really won't be a problem.

CHAIRPERSON FERRIERI: Dr. Kilbourne?

DR. KILBOURNE: Unfortunately, I don't think there's any way to do this in advance of a massive release of virus into the population, because I think the problem here -- Well, basically, you have a cytonecrotizing virus which is not temperate, in any

sense. If it's replicating in the respiratory tract, no matter at what level, 10^2 or 10^6, it's destroying epithelial cells.

It also has direct effect on polymorphonuclear leukocytes, which hasn't been mentioned in terms of the pathogenesis. I think the further point is that we have different levels of bacterial colonizations in different populations at different times a year. So I think that there has to build up quite a big experience to really test this.

My first encounter with influenza virus professionally was in 1947 at Ft. Monmouth when the so called FM-1 strain emerged, so called mild strain of virus. I have in my pocket a slide I could show you, if time permitted, and probably doesn't, showing that concomitant with the subsidence of that epidemic, a direct increase in the number of patients admitted to the hospital carrying group A streptococci followed by an epidemic of streptococcal pharyngitis.

That is wild type virus, but it seems to me that we have to -- This is a very real concern, and I don't know how you address it with a relatively small scale clinical trial on an annual basis.

CHAIRPERSON FERRIERI: Dr. Kohl, and then Dr. Edwards.

DR. KOHL: Peter, I believe when you presented your data -- Dr. Wright -- that you presented data on otitis media in vaccinees and controls, and the statistics were ns on all of them. But it went by kind of quickly, and I think it looked like there were a higher number of otitises trending at least in all the vaccine groups compared to the control groups. Am I remembering that right?

DR. WRIGHT: Yes. In the first year, the p was .3 with, obviously, a rather large end.

DR. KOHL: What was the n in those? You didn't tell us that -- roughly. Hundreds? Thousands?

CHAIRPERSON FERRIERI: It's in the tables attached to the --

DR. MURPHY: It was like 20 -- There were 20 otitises out of about 1,000 vaccinees versus six out of like 450 or so. That's approximately the numbers.

DR. WRIGHT: Yes, that's correct. So one would have had to had to go a good deal larger to demonstrate any kind of a significant effect. In the second year, there was no effect. The p value was .10, and as I think was commented on, there was efficacy in the second year after the second year immunization in the vaccinated group.

That's what I could tell you. I mean, from the available data, I think you could calculate a relative increase -- you know, the upper limit in the relative increased risk.

I think it's quite striking, given that if you look at 24 children who have natural flu, you can find six otitises, and that probably is roughly the percentage of children who experience natural influenza who get otitis, and this vaccine was extraordinarily successful in preventing otitis during the period of reinfection.

So I'm not saying that, if you went to 100,000 people, you couldn't demonstrate an association with otitis, but I'm simply saying that it's extraordinarily rare and would appear to be safe with those constraints.

CHAIRPERSON FERRIERI: Thank you, Peter. Dr. Edwards?

DR. EDWARDS: I think that in the clinical trial that we conducted in over 5,000 people receiving 10,000 doses of vaccine, there were around 250 children that were between the ages of one and 15, and the bulk of the participants in that trial were normal, healthy adults.

We spent considerable effort looking at

reactions that Peter showed you, but also really making certain that, if there were any febrile reactions that occurred around the time of vaccine administration, that people called, that cultures were taken for other agents and looking very, very carefully for other kinds of explanations for febrile illness.

It's quite clear there will be more runny nose. There will be some people who will have a bit more fever, but I think that that was a lot of people to really look at very carefully, and I feel very comfortable that we looked very completely for severe reactions that may be associated with bacterial super-infection after vaccine administration.

CHAIRPERSON FERRIERI: Kathy, could you extend this to your experience with any hypersensitivity reactions, because I want to include that in our discussion on this point?

DR. EDWARDS: No, there were really no patients that I felt fell into that particular picture. So I really don't think I can comment.

I do think it's interesting that we did have one Guillain-Barre in an inactivated vaccine recipient, for what that's worth.

CHAIRPERSON FERRIERI: The issue being, if

you're using an aerosol, creating an aerosol, will those who have egg allergy be at risk, and is there data from your presentation, Peter? My interpretation was that the risk was extraordinarily low, but I wonder if you could comment on this specific point, hypersensitivity to the egg derived live attenuated vaccine?

DR. WRIGHT: I guess I see two components that maybe are, in some way, balancing each other out. I'm reassured by this recent publication, I think, this month in Pediatrics.

Hugh Sampson from Little Rock is the primary author, and also previously looked at MMR where intermuscular administration of inactivated vaccine, which he demonstrated had a component still of egg contamination, did not cause hypersensitivity reactions. Both with MMR and with the flu vaccine, there seemed to be no correlation with a history of allergy to ingested egg or an intolerance of ingested egg.

So one is giving a higher dose in this case of egg protein. One is giving by a route -- I preface all this by saying I'm not an allergist -- that I would not think would be as likely to be sensitizing as the systemic injection.

All of those things, you kind of balance against each other, and you do point out that in Kathy's study and in the large study in young children, there were no immediate or anaphylactic reactions, nor have they been seen in any of the other smaller studies that have been done.

I can't exclude it. One could do the kind of study that Dr. Samson has done with the live attenuated vaccine. He, obviously, has a group of egg allergic patients who have agreed to be in several different kinds of trials at this point.

That would be my only sort of operative suggestion, but I'm really not sure. I think what he would tell you is there's no relationship of egg allergy with hypersensitivity, and to date hypersensitivity has not been a problem with this vaccine.

CHAIRPERSON FERRIERI: Thank you, Peter. Dr. Breiman.

DR. BREIMAN: I guess, with repeated dosage over time, we may learn more about that, but I was interested also in, I guess, a relevant issue in terms of clinical consequence, although it's not hypersensitivity. I apologize if I missed this in Peter's presentation.

What do we know about, especially from, I guess, the Russians, about the impact on immune response when the vaccine is given repetitively, year after year? Is there actually a tolerance that develops as a result of being less likely to see the vaccine virus systemically following, again, repeated respiratory doses?

DR. WRIGHT: That's, obviously, an interesting question and one that was a potential concern. You see a difference, certainly, in the amount of virus replication with the primary administration to young children, as opposed to the secondary administration in young children or the administration in adults, anybody who is experienced with influenza.

There's several studies that I think are reassuring at this point. Probably most reassuring is that the second year of the large trial also showed efficacy, and that data is -- I don't know whether your Committee has heard it, but it's been referenced here, and it is encouraging data that this isn't just a one-time after the primary infection when you get a substantial replication of virus.

In terms of immunogenicity, one of the best studies I know is one that Bill Gruber did in

patients with cystic fibrosis and their families. What happened was in the first year the mean antibody response was clearly higher to the inactivated vaccine, but over three years of successive vaccine administration, in point of fact, the two -- the mean titer of antibody, serum antibody, in these two groups in the inactivated and live vaccine group were virtually identical.

So the live vaccine actually rose slowly over time. The inactivated vaccine showed an initial higher peak and then kind of plateaued.

We don't -- We think that mucosal antibody is important in protection against this virus, and we now have some specific data to bear on that in young children. So I don't know that -- I would not say that -- We have a very rough correlation of protection, and serum antibody titer of one to 32 or one to 40 is protective against infection.

I think that will prove to be different with a live attenuated vaccine, because there are other components of immunity that you're stimulating.

CHAIRPERSON FERRIERI: As an extension of that question, Peter, are there any animal data that might address this point of constant exposure, so that in the Russian populations, say, you would have 15 to

20 years exposure with live attenuated vaccine.

Is there any data from any direction, in vitro, animal, in vivo, that you're going to have induction of tolerance because of the exposure at the nasal mucosa?

DR. WRIGHT: Brian would be probably the best one to speak to any relevant animal data, Nancy to the Russian data. But one of the things that the influenza field has been sort of struggling with over a long period of time is the "Hoskin's effect," where in a school population in Britain there was a suggestion that vaccination over time led to progressively less protection from the vaccine.

This was inactivated vaccine, and that the end result in the unvaccinated group over a period of time was comparable. That study is open to a lot of interpretive debate, and I think so far, either from Kathy's study where vaccine was given over a four-year period with no obvious diminution in the protection afforded and from everything else we know, I think that's not a phenomena that we're at least aware of for anything that's been done so far.

CHAIRPERSON FERRIERI: Dr. Cox, could you comment on the Russian experience?

DR. COX: I don't think there has been

studies done over longer periods of time than the Vanderbilt study in Russia where immunogenicity was monitored. So I don't really think there are Russian data relevant to answer this question.

CHAIRPERSON FERRIERI: Dr. Edwards, do you wish to add further to this point? Dr. Wright has referred to your studies over a period of four years. Is there anything you would wish to add?

DR. EDWARDS: No, other than I started out with black hair at the beginning of that, and look at me now.

DR. KOHL: What's the control?

DR. WRIGHT: I started out with hair.

CHAIRPERSON FERRIERI: Well, we'll have to do an in depth study here.

Yes, Dr. Huang?

DR. HUANG: I've been forced by the gentleman to my right to ask this question, and that is whether the cold adapted -- the Honorable Gentleman on my Right -- whether the cold adapted strain has any relation to Reyes Syndrome, if that's known, and if taking aspirin causes that.

CHAIRPERSON FERRIERI: Who would like to answer whether the CA strains have any relationship? Do we have any data over a period of years?

DR. WRIGHT; No, we have no cases of Reyes syndrome. We have not used aspirin, and would not recommend aspirin after the administration of this live vaccine, particularly with a B component.

CHAIRPERSON FERRIERI: Very good point. Go ahead.

DR. MURPHY: In response to that is that, looking at rare complications such as Reyes syndrome which is rarely associated with influenza virus infections, clearly associated but it's rare, it's very difficult in limited trials to get information on that, as you are aware.

I think the only relevant sort of vaccine related experience that relates on the effect of vaccination on rare sequelae or rare responses to infections is the studies with SSPE, the live attenuated measles virus vaccine when it was introduced.

It has clearly and unequivocally reduced the incidence of SSPE, and I think that, when we're looking at long term consequences with rare events that are associated with wild type infections, I think the precedents would suggest that they are less likely to occur following use of a live attenuated virus vaccine, but it is something that needs to be looked

at and evaluated.

CHAIRPERSON FERRIERI: Thank you. Mrs. Cole?

MS. COLE: Wouldn't Pepto Bismal have to be included as well? That's considered one product that can also cause it and, when a child has got the flu, if they're throwing up or have diarrhea, that would probably be one of the first things that Mom is going to grab.

DR. WRIGHT: It does have aspirin in it. So it would be --

MS. COLE: That would have to be --

DR. WRIGHT: -- excluded.

MS. COLE: Yes, but that's not really made clear to the public, that Pepto Bismal can also be considered to produce the same effect that aspirin can, Reyes syndrome.

DR. WRIGHT: Right. I think that's probably true. Physicians don't prescribe Pepto Bismal a lot, but I know that it is --

MS. COLE: I'm not talking about prescription. I'm --

DR. WRIGHT: -- obviously on the shelf and is used.

MS. COLE: Yes.

DR. WRIGHT: It's used by parents, but probably relatively infrequently with physician advice. But that doesn't get away from the need to increase awareness.

Reyes syndrome is very curious. We simply have not seen Reyes syndrome for at least ten years, and it so disappeared that to attribute it entirely to the change in prescribing habits vis a vis not using aspirin may not be correct. It just simply disappeared.

It came, and many diseases do this, and then it went away again. Clearly, it was associated with the use of aspirin, and the advice about not using aspirin with influenza and influenza-like illnesses is very rational and should be followed, but that is also to say still that probably some aspirin is being used, and we're simply not seeing Reyes syndrome. Other pediatricians may want to comment.

CHAIRPERSON FERRIERI: Thank you. Any final points before I sum up on this issue? Dr. Kilbourne, you'll have the last remark.

DR. KILBOURNE: There's been no comment yet that I've heard about the immunosuppressed members of our population who are growing in number at both ends of the age spectrum. Dr. Wright mentioned some

studies in progress on HIV, and I think it would be most illuminating to wait for those results.

It's already been demonstrated -- I think Nancy Cox is one of the authors with Alan Kendall -- that in an immunocompromised child your mutation rate of the virus is greatly enhanced, and you get the evolution of new genotypes.

This has been seen, of course, earlier with poliomyelitis in the live vaccine. I think I'd just like to be sure the Committee distinguishes between the different possible uses of the virus -- or the vaccine.

Will it be limited to certain populations? Will it be a supplement to the current vaccine, in addition to, in other words, as a tandem immunization? Will it complement inactivated vaccine? Will it be replacement for inactivated vaccine or will it simply remain as an alternative stratagem for immunization?

Seems to me that much depends on the decision that one makes about the use of the vaccine before one goes into the other considerations.

CHAIRPERSON FERRIERI: Those are all important points, Dr. Kilbourne. They are out of the purview of what we've been given to examine today. I think that we should address those issues at sometime

in the future, if FDA wishes to present them.

I do not wish to suppress interest in your question. I think we should be thinking about those issues in order to bring ideas to some future convening of a group that includes experts like yourself.

So in summary on the last point challenged by Dr. Levandowski, we've not heard -- No one here has brought up data that would suggest that the clinical consequences are evident, any adverse events, nor any clinical consequences in the data available to date on the live CA influenza virus vaccines.

At this point, I would like to open it up for any audience participation or questions. We do have a few more minutes, or anything further that Dr. Roland Levandowski would like to say.

DR. LEVANDOWSKI: Well, I would particularly just like to thank the Committee and experts for all of the very helpful comments, and also our speakers earlier this morning for some very excellent presentations.

I think this has been exactly what we've been hoping for in terms of getting some of these issues discussed and getting opinions of the broader

medical community to help us in our thinking about what we should be looking for.

CHAIRPERSON FERRIERI: Thank you, Roland.

Again, is there anyone who would like to say something from the audience? One, two, three.

Well, thank you all for a very wonderful session, and we hope to talk about this issue again.

Thank you, Committee members.

(Whereupon, the foregoing matter went off the record at 12:24 p.m.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: CENTER FOR BIOLOGICS EDUCATION AND RESEARCH VACCINES AND RELATED PRODUCTS ADVISORY COMMITTEE MEETING

Before: FOOD AND DRUG ADMINISTRATION

Date: NOVEMBER 20, 1998

Place: BETHESDA, MD

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.