probably need between 110 and 170,000 kids to be followed up to find significant results here.

I mean, this could be a couple of years of enrollment if the whole VSD population starts using the vaccine, or it could be much more if their take takes more time. This could be very well all infants by the inclusion of other HMOs.

I don't know if Melinda Wharton would like to comment about this or somebody else from CDC.

And this is very quick and dirty. There is no consultation or discussion on sample size officially yet.

CHAIRMAN OVERTURF: Dr. Wharton.

DR. WHARTON: Well, just to build just a little bit on Dr. Izurieta's comments, what happened in the study that Dr. Komars has published in Pediatric Infectious Disease Journal, because there was not widespread use of RotaShield in the participating VSD sites back in 1999, there was a study rapidly initiated involving a large number of managed care organizations that had the same type of electronic records or computerized records available

to the VSD sites, and that was pretty rapidly implemented in response to the signal.

So if the VSD sites are not participating yet in the program, the other ways that ascertain that in populations that are using the vaccine could be developed, although I think pretty difficult to rely on that for a routine study. This was done in an emergency setting in a very resource intensive way, and I think we wouldn't want to rely on it for a more routine ascertainment.

CHAIRMAN OVERTURF: Yes, Dr. Malonardo.

DR. MALONARDO: I would like to ask a question to the FDA and the people in CDC who work on these, and please understand my bias. I don't work in vaccines. I work in drugs, and when Dr. Izurieta actually said that for RotaShield there was an opportunity to detect a risk of one in 10,000, I was very impressed.

So there must have been a tool already back then that had the ability to discriminate even in these very small numbers. So do you have a sense that for what Merck has proposed and what you are

planning to do with the VAERS, the VSD and the study from the sponsor? Have you increased the possibilities of even improving into what's been pharmacoepidemiology in the past?

In other words, are you better suited now to either at least detect that risk that RotaShield had or improve on that number?

DR. WHARTON: Well, in terms of the basic vaccine safety infrastructure, which the Public Health Service maintains at CDC and FDA, the vaccine safety data link is really the primary piece of that ability to ascertain that level of risk by using linked electronic databases in large managed care organizations where you're able to capture both exposure and outcome in a relatively efficient way.

These associations can be identified and then chart reviews can be performed when needed. It still ends up being a -- it still can't be done immediately. It still requires a lot of planning and work, but compared to performing a clinical trial, it's a vastly easier way, an observational study where you end up having to recruit and then do follow-up

without the infrastructure that these computerized databases provide.

DR. BRAUN: Can I?

CHAIRMAN OVERTURF: Please introduce yourself.

DR. BRAUN: Yeah, Miles Braun from FDA.

I'd like to address that question in two ways. One is I think since the RotaShield experience, the VSD has expanded to include a few more HMOs, or managed care organizations. So that increases the amount of subject under potential study. So that's one thing that's different.

Now, the other thing, I think, that we can improve on, and Dr. Izurieta alluded to this, is that I believe in the RotaShield experience, the VSD sites overlapped with the Phase 4 study. So the Phase 4 study was going on in an HMO that was also part of the VSD.

So in a certain way you're double counting the same people, and I think what Dr. Izurieta was saying, and which, you know, I think we would support, is the CDC has invested in that infrastructure. It

exists, and I think it would be desirable that if there is going to be another study done, and this is what the sponsor had proposed, that it be done in a way that it doesn't overlap so that you're not studying the same patients in the Phase 4 that you have in the VSD because how much really additional information is there.

So those are, I think, two ways. One way we have improved with the VSD because it's expanded, and this is on the table, I think, today, this overlap issue .

CHAIRMAN OVERTURF: Dr. Malonardo.

DR. MALONARDO: Yes, just a follow-up.

So that means that you hopefully will be equipped to detect the risk of at least a one in 10,000 or even actually even smaller, because you're improving whatever tools you had in the past. So that's -- okay. Thank you.

CHAIRMAN OVERTURF: I guess I'm a little bit confused by that because obviously in a post licensure study, particularly in the VSD study, I guess there will be a small control group. It depends

a little bit. It depends a little bit on what's recommended for the vaccine if, indeed, it is licensed because if it's licensed for a routine use, then at least theoretically the only people getting -- nearly all of the children will be eligible and will end up getting vaccine. The only control group will be those for whatever reason, missed vaccine. That's the group that you'll be comparing against?

DR. IZURIETA: You['re right. Choosing the right control group is going to be a challenge with reality. In some VSD studies, historical controls have been used. In other VSD studies other HMOs who have not used the vaccine or the product have been included. We could use different background estimates from different groups. I don't know if Melinda has additional.

Right, you can use case series analysis, which is very efficient, if you study, you know, a window of exposure and then a window of nonexposure, and that has been done with RotaShield and with other products. That's probably the most refined way of doing it.

But, again, if you do rapid cycle analysis, then there are certain ways you can do it. You cannot do it in this particular way.

So to be VSD efficient, it can be done. It depends on how many resources you invest, how much you are going to do, how far you want to go, but it can be done as Melinda said.

CHAIRMAN OVERTURF: All right. Dr. Markovitz.

DR. MARKOVITZ: Yes, I just wanted to echo a couple of comments. First of all, what Dr. Karron was saying about the seizures.

I'm not sure I understand why that happened or if it really is anything, but it certainly looks like something to emphasize in any post licensure follow-up that takes place.

Also, just echoing what Dr. Overturf said, certainly there's a lot of room for studying people who have various types of immunosuppression, and I'm glad to hear that the sponsors are planning on doing that because obviously that will be important both in terms of whether to vaccinate those vulnerable groups,

as well as the concern about the vaccine being shed to those vulnerable groups. So in both ways it will be very good to get those data.

And speaking of groups not yet tested, this is a recurring theme, but I think that the sponsor has been very thorough in most ways, but really the vaccinated population in these studies, again, doesn't reflect that of the U.S. Very low on people who are African American, very low on people who are Hispanic, and very low on people who are Asian. And I don't think that this is the best way to conduct these trials.

I don't think it obliterates the meaning of the trials or anything, but I think that more effort has to go into having these trials actually represent what modern America actually looks like and not for political correctness reasons, but rather for vaccine efficacy reasons.

CHAIRMAN OVERTURF: I would like to ask one other question. You know, are sera still available to reevaluate this issue of serological interference? And are there plans to actually relook

at the sera?

Because there was this question about an unvalidated assay for the pertussis antigens.

DR. HEATON: Yeah, the question about whether sera is still available. We actually had sera from the original group that was tested, and we have run pre and post immunization titers in a different laboratory.

Although I guess I just want to back up and say that the assays in the previous laboratory have been validated, and we have reviewed those assays, and I think FDA though is still going on with their review of those assays.

But doing repeat testing and then we're also testing another subset of kids within the REST study where we had sera available, and then in addition, we will have another concomitant use study with the Pertactin containing vaccine and that we need to do in Europe as well. So we'll have data from that study.

CHAIRMAN OVERTURF: Yes, Dr. Gellin.

DR. GELLIN: The background material and

the presentation, I think from the FDA, highlighted that there was some discrepancy about numbers. I guess I'd like to have some understanding of what that's all about, and what the implications of that might be.

DR. KOU: My name is Jingyee Kou. I'm the statistical reviewer for this product.

Actually the discrepancies on efficacy looks as just differences in numbers, but it's a long story behind it. What happened is that when we get an application from sponsors, usually they submit two sets of data. One they call it raw data, listing data, which has individual subjects, and then they have what they call analysis data, which is derived from raw data.

And so this is a miscommunication that Merck believes that FDA only uses the analysis data, and it happens that we use both, and then I'm the one that believes that I wanted to arrive at the same conclusion as the sponsors from the raw data. So I worked with the raw data.

But because Merck believed that we only

work with analysis data, so they didn't provide as much detail as they had with the analysis data, and also because the size of the data set, and by the time I realized I didn't have certain crucial information and asked them for it, the timing is already.

And so that's the reason why you see the discrepancy. This happens; when we review data, it happens. You know, it just happened this time that I can't make it before and we can resolve the difference between the two before this committee meeting.

But I have to say the difference, like I said, I don't really know at this point because we still need to communicate with Merck to really fine tune, to find out where the difference are, but I think one of the possibilities how to handle missing data, I delete all the missing data, but then there are different interpretations and so that's one thing that I would like to look into.

But the thing is that if you look at how my number is different from Merck's number, it's in the same -- the reason that we get to the same efficacy estimate is because we apply -- I mean, at

least I feel comfortable because we both apply the same criteria to both arms, both vaccine and placebo arms.

So even though my numbers are different, are lower than theirs, but they're lower on both arms in the same fashion. So that's why I come out to have the same efficacy estimate, even though the number of cases are different. That's probably just due to we have this disagreement on which ones we call a case.

I hope that --

DR. GELLIN: So we're asked a big question about efficacy. Is this interesting or is it relevant is the real question.

DR. KOU: Well, okay. So if you have my briefing document from, you know, a month ago, which I was still working on, at that time I was not comfortable with the number because the discrepancy is not in any fashion, and then I realized the reason is because I didn't have the crucial information for the rotavirus season for each of the sites, and so I couldn't determine when the first rotavirus season was over. So, in other words, it ends.

This time, and after we have communicated with them, that information was provided. So this time when I look at the number, and like I said, even though the number of cases are different, I mean, yes, that's important, but in terms of the efficacy itself, I felt, you know, comfortable that number will not change dramatically.

So for 006 they have the hypothesis is great than 35 percent for the lower bound and for the 007 it's zero percent. I would say it's highly likely that it will meet those criteria.

CHAIRMAN OVERTURF: Yes, Dr. Wharton.

DR. WHARTON: I just want to follow up on the question Dr. Self asked earlier about the burden of disease and likely impact of the vaccine on public health. The figure of one in 65 children being hospitalized I've heard often cited, but it has never been clear to me whether or not there were risk factors for hospitalization that, in fact, have been identified.

And if the risk factors for hospitalization are the same as the risk factors for

not being vaccinated on time, we may, in fact, not realize the full benefits of this vaccine, given the relative narrow window in which the vaccine series needs to be administered.

CHAIRMAN OVERTURF: Do you have any information in terms of the nine months of the previous vaccine what the uptake was?

That was a vaccine which was recommended, I believe, by ACIP as well as by American Academy for routine immunization for children. Do you have any idea in that first nine months whether the uptake was comparable to other vaccines in the first nine months?

DR. WHARTON: Yeah, although the vaccine was really pulled during the ramp-up phase of introduction. So I'm not sure that's a comparable experience. Really the issue I was raising didn't have to do with recommendations. It had to do with our ability to deliver vaccines on time to children who may be, in fact, at higher risk of serious consequences due to rotavirus, although I don't know that. I mean, I've never actually seen if the data exists about risk factors for severe outcomes due to

rotavirus. I'm not familiar with it.

CHAIRMAN OVERTURF: A lot of that data is from the CDC's groups, from Roger Glass, but he's not here I take it.

Are there other comments before we proceed to the other questions? Yes, Dr. Gellin.

DR. GELLIN: This may follow from OPD experience, but what are the recommendations if the infant spits this stuff out?

DR. HEATON: So the question is what are the recommendations if the infant spits the vaccine out. We do not recommend to repeat the dose because if they spit it out, we don't know how much they've still maintained, and in fact, all of our efficacy data is just based on not repeating the dose and keeping those kids in the efficacy analysis. So it does take that factor into account.

CHAIRMAN OVERTURF: Are there any other comments, particularly in regard to Questions 3(a) through 3 -- I've made it now 3(e) because I added seizures to that group that need to be examined carefully.

For those of you who are not pediatricians, seizures is an extremely difficult problem to deal with in that age group. It is not as easy to diagnose seizures in small infants as one would guess. So I suspect that that's a very difficult issue to deal with. It's not as straightforward as it perhaps sounds.

Any other comments? Dr. Word.

DR. WORD: I don't know if this goes under your pharmacovigilance or does it go up into the safety, but I think as Dr. Wharton pointed out, pediatricians are generally trained to always do catch-up immunizations, and if they only have data up to 34 weeks of age, what are you going to tell someone if someone walks in the door at four months? Do you still go on and give that three dose series or do you say, "Don't worry about it"?

And I don't know what area -- because I think that's one of the questions I had, but you asked it already. So I didn't need to repeat it.

CHAIRMAN OVERTURF: I think that's the point made by Dr. Wharton, and I think it has to be

part of the post licensure studies, which is to look at how you extend the dose interval, as well as beginning the series. It has to be a critical feature, not only its effect on safety, but also its effect on effectiveness has to be part of those studies because this will continue to be an issue with providers until that information is complete.

CHAIRMAN OVERTURF: Any further questions?

(No response.)

CHAIRMAN OVERTURF: Well, I think without further ado, we'll go ahead and begin to consider the other questions, and we will take votes on the first two questions.

And so I'll ask the first question first, and then ask each member of the committee to address the question. The first question is: are the available data adequate to support the efficacy of RotaTeq in preventing rotavirus gastroenteritis caused by serotypes G1, G2, G3, G4, and G serotypes that contain P1, for example, G9.

When the two doses of vaccine administered at six and 12 weeks of age -- excuse me -- when the

first dose of vaccine is administered at six and 12 weeks of age followed by two subsequent doses separated by four to ten week intervals; so the dosing intervals are very specifically specified in that question, and the time of initial dosing.

So I'll start with Dr. Markovitz.

DR. MARKOVITZ: Back to first. Well, fortunately this one seems pretty easy to me. I think that this vaccine looks highly efficacious. I don't see any holes in the presentation in terms of efficacy. So I would vote yes. It certainly satisfies those criteria.

CHAIRMAN OVERTURF: Dr. Farley.

DR. FARLEY: Well, I guess we didn't spend a lot of time looking at the serotype specific data, and I guess there are some holes there that kind of cross over, that if you look at it by just efficacy against disease, what is it? That maybe the numbers weren't there for three, four, and nine, but then if you look at hospitalizations and ER visits, it fills in those gaps.

So, I mean, I think it's the composite

data, and since most of the disease is G1, that there is a comfort zone there. I mean, I think that by inference that the P1 containing ones other than G9 might be covered. So I'm not sure if we need to get down into that detail, but overall, you know, I think the efficacy data -- and I think we have to emphasize the time of administration being very tightly studied and our recommendation would be to keep it tightly linked to those age groups for now at least.

So I guess I vote yes.

CHAIRMAN OVERTURF: Dr. Royal.

DR. ROYAL: I would also vote yes as well. Certainly the data show that preventing infection in a significant number of these kids will prevent secondary complications. Again, you know, these vaccines or the infection itself, the primary effects of the infection are not what damages intestinal tract, and to a large extent, increased surveillance does have an impact, but certainly the vaccine itself by preventing infection certainly carries a tremendous benefit.

So I would vote yes.

CHAIRMAN OVERTURF: Dr. McInnes.

DR. McINNES: I think the data presented do support efficacy against rotavirus gastroenteritis of any severity and against severe rotavirus gastroenteritis caused by vaccine serotype at the ages and within window as presented in the question.

CHAIRMAN OVERTURF: Dr. Wharton.

DR. WHARTON: I agree that the data supports efficacy for prevention of rotavirus gastroenteritis using the study or the schedule that we studied.

CHAIRMAN OVERTURF: Dr. Gellin.

DR. GELLIN: Yes, I agree as well that the data support the efficacy. Interested given the global reach of the disease and the vaccine to continue to look for emerging serotypes and how the vaccine does against them.

CHAIRMAN OVERTURF: Dr. Word.

DR. WORD: I think I too would say that the data they presented does support the efficacy. I guess I'm a little challenged with the term "severe" versus just general efficacy because I still have a

problem with that table and how things were calculated because when I do my math, when I get down to a number of less than 16 and it's not severe but I've had a seizure, I'm troubled.

But I am satisfied to say that it's efficacious, and they've proven that.

CHAIRMAN OVERTURF: Dr. Malonardo, you're not a voting member, but you can give an opinion if you want at this point.

DR. MALONARDO: (Speaking from an unmiked location.)

CHAIRMAN OVERTURF: Okay. Dr. Karron.

DR. KARRON: Yes, I believe that the data are adequate to support the efficacy with the schedule as specified.

CHAIRMAN OVERTURF: Dr. Self.

DR. SELF: I vote yes and just note that what we're voting on is not the type specific, but it's the overall, including all of those types just per a comment earlier.

I guess I'd also like to commend the sponsor on putting together a very coherent and

comprehensive program. I wouldn't say it was a joy to review, but it was a pleasure.

(Laughter.)

CHAIRMAN OVERTURF: I also would assert that I think the efficacy is well demonstrated by what was I think a relatively exhaustive trial, an I congratulate the sponsors on that as well.

I think the biggest issue is obviously when you do a large trial like this, one requires in a prospective fashion doing it under ideal conditions, making sure that every trial gets started and given exactly a specified time. That may be very difficult to accomplish in the public health scheme and will have to be worked out in post licensure studies, but I also vote yes.

The second question there may be a little more debate on, is are the available data adequate to support the safety of RotaTeq when used in the three dose vaccine series beginning with the first does at six to 12 weeks of age, followed by two additional doses separated by a four to ten week interval.

And so we'll start on the other side at

this point and ask Dr. Self to begin answering that question.

DR. SELF: My answer is generally yes, although there are a few safety issues that I think merit follow-up in the post licensure studies. The main issue, since this is all sort of conditioned by the issue that the RotaShield vaccine had I think are the rates of intussecption and the possibility that there are some excess cases that are caused by the vaccine.

In trying to reconcile these two, just a back of the envelope calculation of the efficacy to reduce hospitalizations in the first couple of years of life net of some bound based on a relative risk bound that can be achieved either in this study or in the follow-up studies can be computed, and if I've done this correctly, that net efficacy of hospitalizations is still around 80 percent, down from 75 or 95 percent, but still very substantial.

And so in trying to grapple with the balance between risk and benefits, it does seem to me very clearly to be in favor of the vaccines.

CHAIRMAN OVERTURF: Dr. Karron.

DR. KARRON: Yes, I do believe that the available data are adequate to support the safety of RotaTeq. However, I do as we have all discussed think there are important issues to be addressed post licensure.

I think it's important to look at rates of intussecption after each dose and particularly stratifying by age of the recipient at each dose. I echo Dr. Wharton's comments that in the real world things may be very different.

I also think it's important to continue to collect data on seizures as we've discussed previously.

CHAIRMAN OVERTURF: Any comments, Dr. Malonardo?

Okay. Dr. Word.

DR. WORD: Actually, I actually agree that they provided adequate, sufficient data to support their safety and would probably echo some of the same concerns because I think before we have the big red flag that went up with intussecption, and it has been

such a focus there because of the way it's administered, but as seizures popped up, there may be other things that we'll begin to see. So I think it's realistic in post licensure to begin to pay close attention to some of the other things, and I think seizures was interesting to look at.

CHAIRMAN OVERTURF: Dr. Gellin.

DR. GELLIN: Yes, I agree that the data do support safety with the caveats of 3(a) through (e) as now articulated as the follow-up studies, and would encourage that to the degree that these can be done as this vaccine reaches into the developing world, that there be aggressive studies to look at safety in the developing world applications.

CHAIRMAN OVERTURF: Dr. Wharton.

DR. WHARTON: I agree that the available data support the safety of RotaTeq when used in the schedule that we studied, although as other panel members have stated, I think it would be important in the post licensure period to look at both seizures and intussecption.

And, again, echoing earlier comments, the

vaccine is likely to be used in different ages, which will raise its own set of safety issues, and these will have to be addressed post licensure.

CHAIRMAN OVERTURF: Dr. McInnes.

DR. McINNES: I'm left feeling a little bit uncertain about safety, and yet one side of my brain keeps asking me why, and I think when I go and I look at the data and I look at the -- I agree that it doesn't seem to be clustering with the intussecption either in that seven days or in the 14 days, and those 52 day winter results around that post dose two leave me a little bit uncomfortable.

And why am I uncomfortable? I'm uncomfortable because I remember what we lived through with a different vaccine, which I completely appreciate. It's not your product, but unfortunately, it's our collective problem, and I realize also that if you increase the window out to 60 days, you know, you change that four to one to five to two and things start to look better, and that there's really no apparent pattern emerging for when these cases occur after each dose specifically if you go and you look at

a little bit bigger window than that 42 day.

I'm still left with an uneasiness that I would agree that I think your data don't specifically point to a safety issue at this time, but I really am concerned about the age at which children are going to get immunized and what is a relatively broad window that was both inclusion criteria and window around each vaccination.

So that in fact, you can land up with children being quite old when they're receiving some of their doses, and that's within the clinical trial setting where they would not have fallen into protocol analysis if they were outside of the window.

So I think the implementation piece of this is going to be quite a challenge, and it may not be one for the label, may not be one for VRBPAC, but certainly it's going to fall to our ACIP colleagues down the line, and I wish there were additional data to help in what is going to be a decision making process around the recommendation and implementation piece.

So the data driven part of my brain says,

yes, I think the safety data look good, but the other part of my gut is just wishing there were some other data either not right now, but that would be coming to help these really very difficult public health decisions about implementation.

We cannot have another -- I don't think we can afford another problem with replicating attenuated vaccine for rotavirus.

CHAIRMAN OVERTURF: Is that a no?

DR. McINNES: It's not a no. I'm going to default to the data part of my brain and leave my gut out of this, but I just wanted to put that focus back up on the table.

CHAIRMAN OVERTURF: Dr. Royal.

DR. ROYAL: I would agree that the data do support the safety of the vaccine. However, I do feel some uneasiness about the potential for the occurrence of intussecption in the post licensure period, and of course, support the data collection that's going to be done, as well as the development of a comprehensive way planned for looking at this issue of seizures, given the fact that you have a live attenuated virus.

One must be concerned about such things as aseptic meningitis and other issues that really should be looked at beyond just collecting the numbers of cases.

CHAIRMAN OVERTURF: Dr. Farley.

DR. FARLEY: I think just to make a comment that if this were a disease that was highly lethal or had, you know, serious long-term morbidity in the United States, that we would not be questioning a clinical trial that enrolled 72,000 children showing safety. I think that's part of the struggle here, but I think within the parameters of this study, that includes the strict schedule, the age groups studied, and those who were excluded from study that safety has been shown. So I would vote yes. I would put in just a couple of comments that are somewhat redundant, but I would caution the next committees and advisory groups who have to deal with the recommendations for usage that caution or caution them to give a great deal of thought to catch up recommendations, if any are given, and also with the populations that have been excluded from this and how the recommendations will be formulated for those particular groups.

And I would also very much support further studies for how best to document safety for the use of this in developing countries because I think this is a tremendous vaccine for that possibility.

CHAIRMAN OVERTURF: Dr. Markovitz?

DR. MARKOVITZ: Yes, before voting on this, I just wanted to echo one thing Dr. Gellin said because I think he's the only one who so far has said it, and I think it's worth echoing back on the previous question, which is that it is going to be important to continue to have surveillance as to serotypes because if they start to change in any significant way, that obviously could alter future decisions about the vaccine.

Now, to this question, I'm going to try to keep my gut out of the rotavirus discussion, but I think what Dr. McInnes said makes one think that one obviously this is the one the company is doing, the post marketing surveillance, assuming this is improved, that it will be important to focus on kids who are vaccinated at some different time point than what is currently recommended based on the studies.

That being said, and then echoing what everybody else has commented on and I think we've all discussed it at length in some of the other things we need to follow up on, which I won't repeat, I vote yes. I think the safety data are convincing.

CHAIRMAN OVERTURF: Actually, I think the data that were presented to me actually are very reassuring for intussecption. I don't know how you can do better. Obviously you could add another 70,000 patients.

I think we're a little bit a victim of our own success or your success in that regard because there is so much data that a whole lot of things were uncovered, including this issue of seizures as a possible issue.

And as saying this from a clinical standpoint, it's very cloudy issue in that population, and of course, rotavirus has been found in extra intestinal sites, including the CNS on rare occasion. So it's obviously a question that has to be answered, but I'm actually reassured, and I guess I'm not feeling as much with my gut as a few of the people

here.

I think the data very strongly support the safety of this vaccine, as well as can be done at this point, and I think perhaps we all are going to have to live with this back of the head, tentative feeling until we've lived with this vaccine for a while, but I think I would vote yes, that the safety is established for the vaccine as well.

Are there any other questions before we adjourn for the members or the sponsors, the FDA? Any general comments anybody didn't get to put in for discussion of the questions?

(No response.)

CHAIRMAN OVERTURF: I think the meeting is adjourned. Thank you very much.

(Whereupon, at 3:08 p.m., the meeting in the above-entitled matter was concluded.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: Vaccines and Related Biological Products Advisory Committee

Before: DHHS/FDA/CBER

Date: December 14, 2005

Place: Bethesda, Maryland

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.