or comments from committee members about the material that we've seen. We'll then have the open public hearing and then return to the committee for general comments.

So I'd like everybody to think about whether this is a question about the material that they've seen.

I think you were first, and then we'll go over here. Almost everyone has their hand up, and we'll go down the row.

DR. FOST: A question for Dr. Wharton. It has to do with the relative risk and benefit of the RotaShield vaccine in developing countries versus the U.S.

In the U.S. a child with rotavirus infection has a relatively low risk of anything serious happening. There is mortality rate, but it's low, and the rest is relatively manageable complications, hospitalizations.

In a developing country where the risk of death is much higher per 1,000 cases of rotavirus, it's a different potential benefit. My question is this. Have you made these calculations or can they be? Do you have enough data to make them?

Suppose the rate of intussusception in a

developing country were the same as it was in the RotaShield experience in the U.S. Suppose the rate of intussusception was the same, and for the sake of discussion, suppose all of those children died of intussusception.

What would that be, that death rate be, as compared with the death rate of rotavirus infection itself? That is, can an argument be made; is there any data to support the claim or the possibility that even if there was a complete, 100 percent mortality rate from intussusception, you still might be better off if you were in a country where you had a high risk of dying from rotavirus?

DR. WHARTON: In our discussions with the Advisory Committee on Immunization Practices, this clearly was an issue which weighed on the committee. I think that the committee was very cognizant of the fact that conditions which prevail in the United States don't prevail globally, and other countries faced with similar data might very reasonably come to different conclusions about what was appropriate to do in their country.

This was a subject of a WHO meeting which I didn't attend, but my understanding is that it was discussed extensively, and Dr. Snider was there, and

perhaps he could comment more on what happened there, but clearly the situation is different in other countries.

Other countries could reasonably conclude that use of the tetravalent rhesus based vaccine could be of benefit.

DR. FOST: Do you have the numbers? I mean is the question that I asked answerable?

DR. SNIDER: It was not. I moderated the ethics group at the rotavirus consultation, WHO consultation, and we tried to find those data because I think the question you raise is a very important one.

Unfortunately, data on death from intussusceptions, even the incidence of intussusception in a lot of developing countries, is just not available, and so the group felt that they really could not quantitate these risks as well as they would like and recommended that that kind of information be collected.

DR. DAUM: While you have the floor, did you have a question for the speakers, as well? And we're just going to go down.

DR. SNIDER: Yes, and I apologize to my co-worker from CDC for asking this now. I should have

asked it before, but the number that's thrown out of one in 5,000 is obviously an estimate, but that number is also used in some calculations later about a trial that we're going to be discussing.

And I was just wondering. I know it's a conglomeration of risk from dose one and dose two, and it's hard to get 95 percent confidence limits around a risk of one in 5,000, but I just wondered if some thought had been given to how low might it be or how high might it be in terms of what we might have to be looking for in any subsequent trials.

DR. WHARTON: I think that probably is something we should have addressed, but I'm not aware of any calculations of certainty around that estimate.

I would point out though that the findings of the case control study were very consistent with those of the retrospective cohort study also done by CDC. So I think that the point estimates are reasonable as point estimates, but in terms of applying the 95 percent confidence intervals to the background intussusception rates, I'm not aware of that calculation having been performed.

DR. DAUM: I have Dr. Huang, Dr. Faggett, and Dr. Griffin.

DR. HUANG: I was impressed by Dr. Shiels'

comment that intussusception occurred less frequently in less healthy infants, and I would like to give him a chance to sort of comment on what he thinks about that in terms of under developed countries and the discussion that went on just previously about the possibility of continued use of RotaShield vaccine in those countries.

DR. SHIELS: Very interesting question, and at the NIH meeting, the Minister of Health from Peru was present and noted that he sees a much lower incidence of intussusception in the country of Peru than we see in the United States, and I don't believe we have any good data, and we've been looking since that last discussion. There's no good data that correlates exactly the degree of malnutrition in underdevelopment of a country and the incidence of intussusception.

But it is interesting to just listen to at least one minister of health who felt that there was certainly some difference at least in his country, but it certainly does beg the question of the relevance of the number of lives saved by the use of the vaccine weighed against the relative risk of a disease that may be less frequent in that country if they are dying more from a viral infection than they ever would from

a disease that they're not going to solve frequently anyway.

DR. DAUM: Thank you.

Dr. Faggett.

DR. FAGGETT: Dr. Shiels, thank you very much for that very clear lecture. I just wish one of my interns had heard it prior to not giving my eight month old the needed IV in a baby presenting with gastroenteritis, subsequently died from intussusception, age eight months, in July. So it's pretty much as you've outlined.

My question is you mentioned 40 percent incidence, three to nine months of age. That sounds kind of high from my clinical experience in things I've read. Could you comment on that and also at what age did you start seeing them for tissue in the appendix?

You were talking about the studies. So at what age do you start seeing significant lymphoid tissue hyperplasia?

So a two-part question.

DR. SHIELS: Actually a very good question. Again, the incidence of intussusception, the age distribution, I think the best paper that I've seen was authored by Dr. Rennels, and that

distribution did, indeed, fall out exactly as we laid out.

You see the highest incidence in the three and certainly four to nine months of age distribution. Five months of age seems to be one of the highest peaks in all children.

As far as the appendix, the lymphoid follicular tissue, as we have been forced now to grade that in the appendix, we have four grades. Grade zero is seen in neonates, and there's no lymphoid tissue whatsoever.

Grade one is sparse distribution of lymphoid cells not in aggregates, lymphoid cells in the wall of the appendix, and that is seen in the first few weeks of life.

Grade two is when we see defined aggregates of lymphoid tissue. Aggregates are clumps. Those are distinguished from grade three.

Grade three has germinal centers. So the germinal centers will then be the centers of those humeral responses.

And then grade four is a conglomeration of those lymphoid centers and lymphoid follicles that form this conglomerate circumferential distribution of lymphoid tissue.

That spectrum, and we're continuing the number of children that we've investigated. We're going back and looking at every appendix that we've ever taken out of a child, including the tiniest neonates, and those are the most fascinating because in our hospital with a very high risk neonatal population, every time a surgeon goes in to do any intra abdominal surgery, they grab the appendix and take it out and do the child a favor.

So now we have these specimens, and there is this fairly consistent proof, and it turns out there was never proof before we did this, and that was the striking thing that was raised at the NIH. Where is the proof? It pushed us back to the laboratory.

So now we know that neonates are not born with lymphoid follicles. They develop over time, and they develop in the first 12 weeks. Usually in the first eight weeks of life, you see clearly defined grade two aggregates, and then by age ten weeks, you begin to see clear germinal centers. So by ten weeks of age, you see the germinal centers with the humeral potential that's clearly definable on H&E stains.

And again, the role of the appendix -- I didn't mean to go too fast in that discussion, but I was trying to be cognizant of time constraints, and I

think we met those well, but the appendix turns out to be the only marker that we have in all of these children that are going to be surveilled.

If they go to surgery to have manual reduction of intussusception, the surgeons will invariably take out the appendix. So in our surveillance exercises in the future, I would highly encourage us to bank the appendices and look at those if they are available, which they should be available for children who are treated, and depending on the center, the center I was previously associated with there was a 50 percent rate of surgery. We have pushed that in our current institution to ten percent. The national average is hovering at about 55 percent. So we still have of all children that get intussusception for whatever reason, we still have about a 50 percent chance of having appendices to look at and analyze.

DR. DAUM: Thank you, Dr. Shiels.

I have Drs. Griffin, Kim, Kohl, and Brody, in that order. Dr. Griffin.

DR. GRIFFIN: Well, my question is sort of a follow-up to yours and a combined question to Walter, a combined question for Dr. Shiels and Dr. Wharton.

Because if you put together the data that the two of you have and think about the pathogenesis of this disease because the highest incidence appeared to be in the youngest children and the youngest children are the ones that are predicted to have the least lymphoid tissue.

My question would be whether immunizing those children increases the volume of their lymphoid tissue, and therefore, you can make a correlate with inducing an immune response at an age perhaps that the child isn't usually exposed to quite so many oral pathogens and whether one not solution, but one thing to think about in future rotavirus vaccine development would be to push up the age somewhat of when you initiate infection because rotavirus infection per se, the incidence of the disease, is at a somewhat older age. You're basically trying to get all of those doses in before the increased incidence. I'm no expert in rotavirus, but over six months of age or so, I think, is when you start seeing most of the dehydrating diarrhea.

And if there's a mechanism for putting together these pieces of information to help us really better understand how we should be approaching this vaccine.

DR. WHARTON: Well, the question you raise is an excellent one, and it's certainly one that there's been a lot of discussion about.

The first point I'd like to make is I'm not sure that any of us have -- there's been a lot of focus on lymphoid hyperplasia and its potential role in intussusception by serving as a lead point. It's possible that, in fact, the mechanism is something different than that. There's much discussion in the intussusception literature, particularly older literature about the role of motility in causing intussusception.

My engineer husband and I have had a lot of conversations about fluid dynamics and about the role of partial obstruction with flow across it in creating pressure gradients, and there are two things that are needed for an intussusception to occur. One is a pressure gradient. You have to have that pressure gradient which requires flow.

So I think that motility is a possibility as a factor in the pathogenesis, and that would be independent of the presence of lymphoid hyperplasia.

The one area --

DR. GRIFFIN: Is that that children have -- I mean younger children have more motility or

less motility or how do you relate to the --

DR. WHARTON: Well, the point is that it's possible that what the vaccine does is not cause lymphoid hyperplasia, but induces some abnormality of motility, which could then --

DR. GRIFFIN: That younger infants are more susceptible to than older.

DR. WHARTON: Well, I have no data one way or another on age related differences in motility, but I think in terms of pathogenesis, there is another component that we need to keep in mind and not just focus on the presence or absence of lymphoid tissue or lymphoid hyperplasia.

There is one area though in which we do have some data by age group, although I didn't present it in my presentation earlier. In the case control study, we have looked at the odds ratio for intussusception in the prespecified risk windows stratified by age group, and for the first dose, which was the dose associated with the highest risk, the point estimate for children in the one to two month age group for the three to seven day window was 4. -- I'm sorry -- was 27 with a 95 percent confidence interval of 10.4 to 70.3.

For the three to five month age strata

following the first dose, the rate ratio was 24.8 with a 95 percent -- I'm sorry. These are from the case series analysis. These are not odds ratios -- was 15.2 to 40.3, and the rate ratio for six to eight month old children was 16.5 with a 95 percent confidence interval of 8.4 to 32.4.

Those three rate ratios were 27, 24, and 16, and although the confidence intervals are wide, I don't think one can make a case that, in fact, the risk differed by age group.

DR. SHIELS: To follow on that comment, we didn't discuss much about the pathogenesis hypotheses for intussusception. Essentially there are two mechanisms that are hypothesized. The first is the potential mass effect of a lymphoid follicle being felt by the intestine and then carried forward.

The second hypothesis is -- I think it's largely based on some of the work in the mouse by Dr. Hanani -- that showed that the LPS, when injected into the peritoneal cavity of a mouse, will induce a small intestine small intestine or even more proximally, jejunal-jejunal intussusception that does not progress to an ileocolic intussusception and is usually self-reduced by the mouse.

It looks like it's a very different

mechanism. The important point is that it is a mechanism. It's reproducible in the laboratory. So the fact that a lipopolysaccharide can, indeed, induce motility disturbance or, as we best understand it and try to teach, that it is likely a combination of lymphoid inflammation of the small bowel with a reflex peristaltic disturbance or paralysis. The paralyzed segment may, indeed, be grabbed and moved forward with this lymphoid tissue.

My own personal belief is that it's probably a combination of both. It's likely a combination of both. In surgical reports and having been through way too many of these, the surgeons invariably report -- and they call them lymph nodes -- the masses, lymphoid masses, and it's in report after report after report.

So I suspect it's a combination of both mechanisms.

DR. GRIFFIN: So just one follow-up because I'm not personally familiar with the LPS data or model system. That is known to induce since that is an active activator of lymphoid tissue itself, but the mechanism is known to be a motility based mechanism, not an effect on lymphoid tissue.

DR. SHIELS: Exactly, and the

intussusception occurs within hours, and then it goes away. So it looks like it's a very different mechanism, but it's still important to keep in our consideration.

But as far as the age, even if a three week old child has lymphoid tissue there -- there's data to suggest that, indeed, they do -- they have the potential to respond. Then the question that is begged is: will they then generate germinal centers much earlier than a nonexposed infant if they have precursor cells, even one potential B cell, that can then kick into gear and form a colony?

DR. DAUM: Thank you.

Dr. Kim, please.

DR. KIM: I have two questions to Dr. Shiels for clarification.

First is that, if I understand correctly, you indicated that rhesus rotavirus in contrast to human rotavirus is associated with intussusception, again, in outside data from vaccines. Has that been documented in the literature?

DR. SHIELS: Has the lack of association of rotavirus?

DR. KIM: No, no.

DR. SHIELS: The wild type?

DR. KIM: No, no, no, no. What the question is, that you indicated -- I think you stated that wild type rhesus, a rhesus rotavirus is associated with intussusception in contrast to human wild type rotavirus which is not associated with intussusception. I just want to see whether that difference has been documented in the literature.

DR. SHIELS: Maybe I can clarify it and restate that. If I confused the issue, I apologize.

The data that I have seen published on the wild human rotavirus strain suggests that there is no association with the peak incidence of intussusception graphed over time, over a year, with a clear contrast to the peak incidence of rotaviral infection in that same population over that same time period.

So there is a spike and a very definable peak. The reference I have, I can pull it up, but it's been shared at a number of different meetings. So the wild type and the lack of association has been documented in multiple references in the literature.

As far as the rhesus type, I was referring to the manufactured vaccine, which was a combination of the rhesus and in human strains. That was the reference. So I hope I didn't confuse anyone with that.

DR. KIM: Okay. Second question is I know you talked about lymphoid hyperplasia. Is this unique to intussusception or is this also relevant to other conditions associated with bowel obstruction in infants?

DR. SHIELS: A two-part question. The first part, lymphoid follicular hyperplasia is not unique to intussusception. As a matter of fact, the most common mimic for both intussusception and appendicitis is a disorder known as mesenteric adenitis.

Mesenteric adenitis is definable on ultrasound exquisitely. We can see the lymph nodes. We can measure them, and we can define point tenderness that reproduces the patient's pain exactly.

At the same time, we can see that there is no intussusception, and there is a normal appendix. So there is no specific association or unique association. There's no unique association between lymphoid follicular hyperplasia and intussusception. All lymphoid follicular hyperplasia is is an inflammatory response to many, many different inciting agents.

DR. DAUM: Dr. Kohl, please.

DR. KOHL: Dr. Shiels and Dr. Wharton,

thanks a lot for those presentations.

The question that kind of came up before, but I want to hit it again: the Rennels paper and then wide quoted by many people suggests there's no seasonal association in intussusception. Dr. Shiels you mentioned that not only was there a summer peak, but there was a slight winter peak.

And then in this month's Pediatric Research to be presented, I guess, at the meetings this week in Boston, there is an abstract suggesting that there was a winter peak with intussusception as there was in rotavirus, and it's from the South Atlantic, one of the institutions.

Could you hit some of that data, both of you, a little harder to convince us that there is an association, there isn't an association, or we just don't know at this point?

DR. WHARTON: The sort of ecologic studies that compare the two trends, of course, don't establish that no cases of intussusception due to wild type disease. Dr. Rennels' paper is the one published source that I'm familiar with where there was, if anything, modest late spring, summer seasonality observed in the New York State Hospital discharge data in contrast with the very marked winter seasonality.

That clearly doesn't establish that wild type rotavirus does not cause some cases of intussusception. It simply cannot account for the majority of them.

The studies that have been done of children with intussusception to try to define viral etiology are few and most of them have poorly characterized series of patients and are not necessarily using optimal methods of detection of all potential pathogens, including rotavirus.

So I would consider it unclear whether or not wild type rotavirus can on occasion result in intussusception. It's not clear to me, and I think it's an area of interest and there, in fact, are studies being launched that will attempt to address that.

DR. DAUM: Is there other comment on Dr. Kohl's question?

DR. SHIELS: As far as the seasonal incidence of intussusception, the best reference that we have used actually comes from Scandinavia, from Sweden, and this is literature that was vintage 1980, 1978.

Dr. Ole Ecklof with a large series, and at that time Dr. Ecklof was the world authority on

intussusception diagnosis, treatment, et cetera, and there were two peaks in the Swedish country or the Swedish region.

As far as my own personal experience, I would have to say in now more than a decade of looking at intussusception at large centers, and the largest centers in the United States for intussusception happen to be clustered in that mid-continental region between Chicago, Cincinnati, Columbus, and certainly Boston, and the largest center in North America is Toronto. It currently has the largest incidence of intussusception.

But in those five or six centers, we see the majority of intussusception cases being treated. In at least the experience of two of those geographic regions, I've certainly seen in my own personal experience a focal, definable peak in the mid-summertime and then a much lower peak, but another peak in the mid-winter time.

DR. KOHL: And a second unrelated question. We've talked a lot about lymphoid hyperplasia. There are several well known bacterial agents that cause lots of intestinal lymphoid hyperplasia, eosinia, salmonella. Is there any association between those agents and intussusception?

DR. WHARTON: I'm aware of case reports of intussusception associated with several different bacterial agents.

DR. SHIELS: Actually in a few series that went beyond the case reports there is a gamut of agents that are held responsible. The most common are the two viral agents, the adenovirus and enterovirus. Rotavirus was looked at and was discounted in a number of studies, and then the other bacterial agents then came after the viral agents.

So the bacterial agents were held accountable, but to a much lower degree than the viral agents.

DR. DAUM: Dr. Brody.

DR. BRODY: This question actually shifts focus a little bit. It goes back to the last presentation on the question of clinical trials to test safety, and I took quite a valuable point that you made, the importance of having predefined stopping rules in connection with safety. I would think, however, the development of those sort of rules won't have to make an assessment of what is an unacceptable increase in the rate of intussusception and what thought has been given to how to define what would constitute an unacceptable increase.

DR. CARBONE: Actually a lot of thought has been given, but nothing has been fixed on. I think those are currently under discussion right now. It's a very complicated issue, as you have recognized, and we have within the agency been discussing that issue and continue to discuss it, but I can't give you any sort of an assessment.

In fact, part of the decision to bring it in front of the advisory committee was to seek advice in that area, among others.

DR. DAUM: Dr. Fleming was next, I believe.

DR. FLEMING: Actually I had another question, but I'd like to follow up on Dr. Brody and actually Dr. Fost. I think both raised questions that have essentially been unanswered that are critical, which are looking at risk in the context of benefit and trying to assess how much increase, in fact, is something that could be accepted within the context of how much benefit would be achieved, and these are issues we're going to have to be able to more effective address than we at this point have been able to do.

Actually my question is in follow-up to, I believe, Dr. Wharton's projection of essentially 50

cases of intussusception for 100,000 infant years, and I guess I have -- and this would be by diagnostic procedures currently standard in the U.S. I'm assuming. So I have, I guess, three questions related to this.

First of all, could there be under reporting, and maybe Dr. Wharton can comment on that, but first, for Dr. Shiels, could there be under diagnosis, and could there be spontaneous resolution that would be related to the issue of under diagnosis?

Where I'm leading to is if we do a prospective clinical trial and are carefully monitoring and looking, may we see more than 50 cases per 100,000 infant years?

DR. SHIELS: I think the answer is clearly yes, and it's not a subjective guess any longer thanks to great investigators in Toronto for the first time ever, and we've just had little dribbles of case reports about spontaneous reduction of intussusception, and they've literally been onesies here and there. There haven't been even case reports of two.

The group in Toronto took the time and did meticulous evaluation of children with ultrasound and enemas, and indeed did find 17 percent of all

intussusceptions prior to their report, I would suggest, are going to go undiagnosed, 17 percent. So the answer to your question is in my heart of hearts, I believe there's a 17 percent under reporting or under diagnosis of intussusception, and that now with the use of ultrasound, which is really gaining momentum in the past four to five years, now we have the ability to correctly diagnose children that have intussusception.

Unfortunately, not to get into too much editorialization, but there are forces at work in the country that would encourage us not to diagnose children with expensive diagnostic tests. So when you hold back ultrasound to save money, you're going to under diagnose until they get to the point where you need to do an enema or have a surgeon treat them.

But if we have aggressive surveillance techniques, we should find 17 percent more intussusceptions that are going to be spontaneously reduced, but at least we can find them, diagnose them to find them.

But, yes, there is now clear evidence that children can reduce their own intussusceptions. They just bear down, strain, and it goes away. The classic example, the expert self-reducers are well known, and

they are cystic fibrosis patients, and they get intussusceptions into the teenage years, and they'll tell you when they get it. They will tell you when they reduced it, and they'll only come to you after they've pushed and pushed and pushed and can't get it undone.

DR. DAUM: Dr. Verter.

DR. VERTER: Yeah. Actually I would like to follow up on the issue that Dr. Fleming raised about risk-benefit, and in doing that, first let me state that I'm not a vaccine expert. I'm mostly from the cardiovascular world, but I'd like to ask Dr. Carbone and Dr. Wharton if they could possibly clarify some numbers for us.

On your first presentation, Dr. Carbone, there was a slide that had in children under five years of age, and at the end of it it said U.S. deaths, about 20 per year, one out of 200,000. Was the per year per year of age? Because --

DR. CARBONE: No, it was total number, not per year of age. They asked me 20 to 40 deaths per year in the United States in children under five due to intussusception.

DR. VERTER: Okay. Well, that's --

DR. CARBONE: Sorry. Rotavirus. Sorry.

DR. VERTER: Yeah. Due to rotavirus. Okay. So it would be of the one of 2,000 that get rotavirus, that that total, 20 of them, 20 to 40 die.

Well, what I'm trying to focus on is the one out of 200,000, where did that come in. I estimated about 20 million children under the age of five in the United States. Okay?

And one out of 200,000 would give me about 200 deaths. So I'm just trying to get a sense of what you're relating it to.

DR. CARBONE: Right. The one in 200,000, isn't that the intussusception, not rotavirus?

DR. VERTER: Yeah, yeah.

DR. CARBONE: Right. We're talking rotavirus deaths are 20 to 40 a year.

DR. VERTER: Oh, okay.

DR. CARBONE: And one in 200,000 cases of intussusception. I'm sorry for my perplexed look, but without my calculator.

DR. VERTER: So what you're saying is the rate is one out of 200,000 in intussusception. The 20 is one out of 200,000 intussusception cases.

DR. CARBONE: ** No, no. That is purely rotavirus.

DR. VERTER: Okay.

DR. CARBONE: And the numbers are a little hard to come by. Many of the cases are immunocompromised children, et cetera.

DR. VERTER: Okay.

DR. CARBONE: It's clear that there's an interesting phenomenon of studying rotavirus vaccines in underdeveloped countries where death would be expected to be a much higher rate. The minute you start studying it, it becomes a Heysenberg uncertainty principle because to prevent deaths in rotavirus, you merely need to get to the child quickly and resuscitate or rehydrate the child quickly, which means in a study the death rates fall to zero even in the placebo recipients.

DR. VERTER: Right.

DR. CARBONE: So death from rotavirus is a very moving and very economically medically technology derived figure.

DR. VERTER: Okay. A second issue has to do with how we're presented with data, and I recognize when we're dealing with very low attack rates people tend to go to things like person-years or doses as opposed to children.

And I'm going to try to focus on children here and see if we can come to the -- I guess she's

passing the ball -- to see if we can come to at least some common grounds so that I personally can get a better sense of it, and what I'm going to focus on is a slide you put up on the RotaShield vaccine, which you said an estimated 1.5 million doses were administered in about a year's time.

And I'm grossly estimating that's about 500,000 children that got it, although I realize that given the time frame probably not all got all three. So I'm probably underestimating the actual number of children.

In that same slide, you indicated that 15 vaccinees reported intussusception, and then Dr. Wharton followed, I believe, by saying that a total of 60 had been reported. So for that cohort, can someone tell me how many actual cases?

DR. CARBONE: One thing to be very cognizant of is when I say 15 cases were reported, that's a passive reporting system VAERS.

DR. VERTER: Okay.

DR. CARBONE: That is no way a surveillance system. So we actually estimate that there's anywhere up to ten times that number of actual cases we see ten percent reported, and again, as Dr. Wharton showed, once the information became public

about the concerns of intussusception and rotavirus vaccination, the number of reports shot through the roof.

So I think we can ask Dr. Wharton directly, but those 60 cases were reported cases, passively reported cases.

DR. VERTER: So are you both indicating that even the 60 is an underestimate of the actual number?

DR. WHARTON: Absolutely.

DR. VERTER: Okay.

DR. WHARTON: It's clear that with passive reporting systems many, many cases are not reported. Even with very severe adverse events that are clearly vaccine associated, reporting is incomplete. So the only question is how bad is it, not is it bad.

DR. VERTER: Okay. So therefore, I can't use any of that data to look at like incidence per child.

DR. CARBONE: Better data would probably come with the study of the large vaccine safety database, which comes from HMO computerized records, and in that case that was the better data.

DR. VERTER: And that did come out to about one out of 2,000?

DR. WHARTON: Well, the retrospective cohort, there was a retrospective cohort study done which involved looking at a large population of children who were vaccinated in a number of large health maintenance organizations, and I don't have those data with me. I can tell you that the rate ratios observed in that study were very similar to those seen in the case control study. The findings were remarkably consistent between the two, but I don't have those data with me.

DR. VERTER: Can I be permitted another one?

DR. DAUM: If it's a brief one because there are people in line.

DR. VERTER: Okay. I'll try to make it as -- this relates to Dr. Wharton's numbers.

You had a graphic which I still see here that I thought was describing some subset of the 427 cases by dose one, two, three during the first 21 days, and roughly eyeballing it and eyeballing it again here, it looks like considerably fewer than the 427 were reported.

If that's correct, does that mean the remaining cases occurred later? And what implication is that for us looking at risk during the entire year

as opposed to the first 21 days?

DR. WHARTON: That graphic showed the onset of intussusception among vaccinated children within 21 days of receipt of any of three dozens of vaccine. As you may recall, only a small number of children in the case control study actually had received rotavirus vaccine. So other cases either occurred outside those 21 day risk windows following doses of vaccine or occurred in children who had never received rotavirus vaccine.

DR. DAUM: Thank you.

Ms. Fisher is next.

MS. FISHER: Dr. Carbone, please correct me if I'm wrong. Did I understand that in your first presentation you said that 12,907 children were studied for licensure of the rhesus rotavirus vaccine?

DR. CARBONE: Those were, right, participants, any dose, any formulation of the vaccine.

MS. FISHER: And there were no cases if intussusception in that study?

DR. CARBONE: In the original studies prior to licensure, there were five reported cases of intussusception. Three of them were reported in children who received non-license formulation, two in

children who received formulated dose. Only two of the five cases were reported to have occurred within two weeks of the dose.

MS. FISHER: Okay.

DR. CARBONE: There were five cases.

MS. FISHER: Then I have two questions, both relating to that and also to the follow-up. If wild type rotavirus is not associated with intussusception and at that point obviously there was no knowledge that the rhesus rotavirus had been associated, what criteria was used to determine that a case of intussusception both in the prelicensure trials as well as the post licensure follow-up, that those cases were due to the vaccine or were not due to the vaccine? What criteria was used?

DR. CARBONE: We used the most conservative criteria, and that was even assuming that the cases were all due to vaccine when they were reviewed compared to the placebo, cases that occurred in the placebo, there was no statistically significant difference. So even if you assume that every case prior to licensure was due to vaccination, if you compare them to the cases that occurred in the placebo recipients, statistically speaking there was no difference between the two groups. So it was not

statistically associated with vaccination.

MS. FISHER: So you were hampered in a way by biological mechanism knowledge because you had to look at only the numbers. So you'd had five in 12,000, which would have been about one in 2,000.

DR. CARBONE: And there was one placebo case reported, but the number of placebo recipients were much smaller, which is why the statistics worked out not to be significant.

And I agree with you. I think in any case, knowing the biology and the pathogenesis of the wild type disease, the vaccine, and the adverse event is always important to have that information whenever possible and to get it if you don't have it.

DR. DAUM: Dr. Brody, please.

DR. BRODY: Just a quick follow-up on the question that was asked about the larger number of cases when you moved away from just the passive reporting. What were the outcomes in those cases of intussusception? Were there any deaths in that group?

DR. CARBONE: There were a total of two deaths reported associated with vaccine that we know of. In one case the autopsy report is not clearly associating the death with intussusception, and the other case there was evidence of intussusception, and

those are the only two cases I'm aware of. That's correct.

DR. BRODY: In addition to death, any other long term serious sequelae from the intussusception in those cases?

DR. WHARTON: I'm aware of one additional child who had a prolonged hospitalization with a number of complications, and I'm not aware of the ultimate outcome of that child, but the child was hospitalized for a couple of months.

DR. BRODY: The reason why I asked this question, because this was not unrelated also to the question of what is an acceptable additional rate because the question is not merely how many more cases you get, but what's the outcome of those cases.

DR. DAUM: Dr. Kohl and Dr. Stephens next.

DR. KOHL: On the other side of the risk-benefit analysis, we've heard the number 20 to 40 death a year in the United States and 55 or so thousand hospitalizations. Are those in the current era, in the last five years, for instance?

Because the oral hydration has really changed dramatically. We used to hospitalize kids like crazy for rotavirus, and now you hardly ever see a kid on the ward with rotavirus.

DR. WHARTON: Those estimates have been developed by the rotavirus group in the National Center for Infectious Diseases, and I think we're hampered by the presence or absence of specific codes and what those codes mean in these large administrative data sets from which these estimates are derived.

The estimates are for the most recent period, but it used to be that there were no deaths specifically recorded as due to rotavirus in the United States because there wasn't a code. Now with introduction of specific codes for rotavirus, some deaths are being identified, and I think that either the deaths could go down as children are perhaps better managed or they could go up as more deaths due to rotavirus are, in fact, reported using a specific diagnostic code, but these are the best numbers we have right now.

DR. DAUM: Dr. Stephens.

DR. STEPHENS: I'd like to return for a minute to the pathogenesis issues of both rotavirus infection and to intussusception. It's my understanding that really children under age three months don't get rotavirus infection, wild type rotavirus infection; is that correct? Could you

comment on the correlates of that protection or someone help me understand that a bit better?

DR. CARBONE: Are you speaking of rotavirus infection or intussusception?

DR. STEPHENS: Wild type rotavirus infection first.

DR. CARBONE: In a developed country like the United States, that's probably an accurate statement. It would be unusual to get infected with that, yeah.

DR. WILLOUGHBY: No. In fact, you can get infected at any age, and there's symptomatic cases going down as low as you want to get. In fact, one of the lead candidates for vaccines has been the fact that in many nurseries there's an endemic strain in newborn, regular, normal newborn nurseries, and that the degree of illness in those nurseries is low, and for that reason those particular isolates have been developed as future vaccine candidates.

So rotavirus replication can occur in an infant at any age.

DR. CARBONE: In terms of frequency, at the --

DR. WILLOUGHBY: Now, in terms if chief burden of disease, typically the rule of thumb is

three months and up. Some people use six months and up. So there's more severe disease once you get a little bit older, but it, in fact, can occur and be symptomatic at any age.

DR. STEPHENS: And the severity of disease in the older children is associated -- is there maternal antibody protection, for example?

DR. WILLOUGHBY: There are maternal antibodies that excrete in breast milk and a variety of animal models. There has been a protection associated with maternal antibody ingested.

The evidence in humans for breast milk protection against viral disease is much less strong than it is for bacterial pathogens.

DR. STEPHENS: The next question relates to the male predominance issue that's associated with intussusception. Was there in the hyperplasia studies, is there a difference between hyperplasia in males versus females?

DR. SHIELS: I can't honestly address that. At this point we did not look at the -- as far as the appendix, we didn't look at the male versus female differences, but it's certainly something we can do.

DR. DAUM: Thank you.

We have only a few minutes left. I'd like to inquire as to several people have mentioned enteroviruses as associations with intussusception in the past. Has either wild type polio virus or polio virus vaccine as represented in OPV been associated with intussusception?

DR. WHARTON: I think there are studies underway to look at that. I'm not aware of any confirmed information in that.

DR. DAUM: Melinda, I guess for you again. Was the vaccine on the market long enough and surveillance in place that was good enough to know whether there was efficacy of the vaccine on the positive side? Was the program working or was it just too quickly flashed to know?

DR. WHARTON: I'm not sure I can address that. Anecdotally we have heard from some people that they did see less severe rotavirus disease during the season in which the vaccine was out,b ut I can't address that further. Perhaps someone else could.

DR. DAUM: Were any of the cases of intussusception investigated insofar as excretion of virus, presence of virus in stool or in lesions, or are there stools stored somewhere where those studies could go on?

DR. WHARTON: There is an effort underway to collect surgical specimens from those children who underwent surgery, including the appendices that were obtained as incidental appendectomies from children who didn't require -- who required surgical reduction, but did not require resection and to look for a variety of viral agents in those specimens.

I think that protocol is still under development. Given that the amount of material available is limited, we need to really make sure that the best use is made of it, but there are plans to do that.

DR. DAUM: Thank you.

I think in the interest of time, we'll truncate this.

Dr. Egan, do you want to make a very brief comment?

DR. EGAN: Bill Egan, FDA.

I would like to ask a question, if I might, of Dr. Shiels. You noted in your presentation that the majority of intussusception that occurs in children, infants occurred at around five months of age, and in the vaccine studies there were a large number of children that developed intussusception at two months.

Could you comment briefly on, one, the difficulties in diagnosing a five month old relative to a two month old, and also the difficulty in treating a two month old versus a five month old and any adverse events, outcomes, relative rates of adverse outcomes in treating a five month old or older child versus the two month old?

DR. SHIELS: Please make sure I stay on target with your question. My understanding is that you are --

DR. EGAN: It's just diagnosis and treatment of a two month old versus a five months old.

DR. SHIELS: Versus a five month old. The bottom line is there's no reason to believe that we should have any lower diagnostic accuracy with a two month old child than a five month old child with diagnostic testing if we get the child under an ultrasound probe or have the child in for a diagnostic enema. There should be zero difference in the diagnosis.

That means that we have to get the child. The issue regarding the potential for increased morbidity and/or mortality in children under the age of three months who may have intussusception is, at least in our experience, related to the thought about

intussusception in a child under the age of three months and the potential delay for diagnosis.

If you're not thinking about the disease in a two month old, then you may not think to do a diagnostic test that's targeted for that, and if plain films are grossly inadequate and you're using plain films as your standard measure, then you may miss the diagnosis until it's too late or until you have to then resect a piece of gangrenous bowel.

So it would be more related to the cognition factor involved in making the diagnosis or at least thinking about it, putting it in your differential high enough to warrant a diagnostic ultrasound or an enema, if that makes sense.

DR. KOHL: Could it be clinically a more subtle presentation also?

DR. SHIELS: Could it be? Anything is possible. Is it possible that the younger children -- there's no good data that I'm aware of that would suggest that children under the age of three months would have the neurologic presentation, as we call it, the lethargy and obtundation felt to be due to endorphins, et cetera, and all of these other humeral responses.

We don't know for sure, but possible.

DR. EGAN: But once diagnosed, treatment and outcome are comparable?

DR. SHIELS: Treatment and outcome should be exactly identical. As it turns out, we have done studies and we just finished our last draft in conjunction with an Army pediatric radiologist. There should be a lower incidence of complication and certainly lower incidence of perforation in a younger child who's undergoing a pressure enema with whatever agent than in an older child. Smaller intestines will perforate at higher pressures. They have more resistive capacity than in a larger piece of bowel.

It's exactly the opposite of what you would intuitively think. So if you infer that and extrapolate that a little bit, you might even say that the younger child should do better with an intestinal obstruction being treated with pressurization.

DR. DAUM: Thank you very much.

We will now move on to the open public hearing associated with this part of our meeting. I believe there's a gentleman -- Dr. Innes, is that you?

DR. KAPIKIAN: No, I'm Dr. Kapikian from NIH.

DR. DAUM: Okay. We're going to call on Dr. Innes first from SmithKline, who has a

presentation that will not exceed ten minutes in length; is that correct?

DR. INNES: That's correct.

DR. DAUM: Maybe less.

DR. INNES: Less.

DR. DAUM: Less is good.

MS. CHERRY: Am I blocking the view when I sit here in front of the screen? Okay.

DR. INNES: My name is Bruce Innes. I represent SmithKline Beecham Biologicals.

I have nine slides to show you to give you an update on the development of our human rotavirus vaccine candidate.

The development objectives at SmithKline Beecham are stated here on the slide. An oral vaccine to protect infants from rotavirus gastroenteritis worldwide.

In particular, we seek a product that profoundly reduces death and hospitalization from severe rotavirus disease, and that achieves cost savings from use of the vaccine in national immunization programs worldwide.

And we've had some experience in working with rotavirus vaccines at SmithKline Beecham. We developed a candidate called RIT 4237 bovine rotavirus

vaccine in the late 1980s. There were initially promising results from the field in terms of its efficacy, but use in the developing world showed low efficacy, and so this program was stopped.

We then concluded that an attenuated human rotavirus vaccine would likely be superior to an animal rotavirus vaccine, and we had an opportunity to in-license on attenuated human rotavirus vaccine strain called 89-12 as a new candidate.

This new candidate has the following history. In 1989, in Ohio there was an epidemic, the usual annual epidemic of rotavirus. These were G1 serotype strains, and it was noted in retrospect that these strains, in fact, elicited broad neutralizing antibodies to the other G types, and in subsequent years provided protection at a higher than expected rate.

And so one of these isolates named 89-12, made by Dick Ward in Cincinnati, was selected for vaccine development. Their strain was prepared as a pilot investigational vaccine by a company then known as virus research institute by serial passage in monkey kidney and was shown in a control trial to be efficacious in children in the first year of life, and I have some of that data to show you, but this also

was published last year in the Lancet.

And then a second year of follow-up in that vaccinated cohort showed that the protection persisted for a second year, and I have some of that data unpublished to show you. So that SmithKline Beecham licensed this product from the renamed company AVANT Immunotherapeutics in 1998.

And in 1999, we began clinical evaluation of an improved vaccine now called RIX 4414 that was made using a refined process.

Here is the year one efficacy of the 8912 precursor vaccine to the product that we are evaluating now, which you're looking at in the columns two and three are the number of cases, and you see that the placebo and vaccine groups were balanced. I've given you a vaccine efficacy estimate, again, several conditions.

Any rotavirus gastroenteritis, and then the severity of rotavirus gastroenteritis is typically graded on a 20 point scale. Very severe rotavirus gastroenteritis is 14 points or higher, and then I've shown you the efficacy against physician intervention and dehydration, and you see that this product was particularly active in preventing the more important forms of morbidity from rotavirus disease.

The reference is down there at the bottom, Lancet 1999.

This is the new information which will be reported in full by David Bernstein and his colleagues at the IDSA meeting this year, but again, we're looking at the same birth cohort with some attrition now down to '91 and '93 in the vaccine and placebo group, and we're again looking at any rotavirus gastroenteritis and then the more medically and economically important very severe rotavirus gastroenteritis, and you see that there was continued protection.

So the overall two year efficacy against severe and very severe rotavirus gastroenteritis was 84 and 100 percent.

So what is this RIX 4414? It's a live, attenuated vaccine. It's monovalent in distinction to other vaccines that are being evaluated. Its serotype is G1, and the VP4 genotype is P8. It shares neutralizing epitopes with G1, G3, G4, and G9 rotavirus types. These represent the majority of human rotavirus strains in North America.

It's an oral vaccine given with buffering, and it's administered by a simple device, and it's planned to be administered as two doses beginning at

six to 12 weeks of age with a second dose eight weeks later.

And the manufacturing process is sufficiently efficient to meet global requirements.

Currently studies with the new product are being performed in Europe, and IND studies in the USA are anticipated to start soon, and then later this year studies in several developing world settings are planned.

DR. DAUM: Dr. Innes, we thank you for your presentation. Oh, there's more.

DR. INNES: One more. We can go through this very quickly.

So what about intussusception? In this particular product, we assess the risk at this point as very low. It appears to be very low. As we have talked about at the meeting today, human rotavirus has no known causal relationship with intussusception, and the major data bearing on this is the disconnect between seasonality of rotavirus in temperate regions and intussusception.

This candidate is a human rotavirus, and in fact, it's attenuated. It ought to have lower risk than wild type rotavirus if there is one, and this candidate differs from animal rotaviruses that were

tested previously in that it's monovalent, not multivalent, if that has any effect, and that is shares only one of 14 genes with the previously withdrawn product.

The other thing we should notice, that the precursor 89-12 elicited a completely different clinical response from the withdrawn product. So far in our testing program, admittedly small, there's been no intussusception in any recipient.

Thank you very much.

DR. DAUM: And now I'm going to thank you and hopefully not in the middle of your presentation again.

We will ask anyone else who wishes to speak at the open presentation to state their name and financial or commercial involvements. I presume we know Dr. Innes'.

And Dr. Kapikian is at the microphone. So I'll ask you to do those things and then please comment.

DR. KAPIKIAN: I'm Al Kapikian from the NIH. Can you hear me? No, they can't hear me.

Thanks for a chance to make a comment. I have a comment and a question for Melinda Wharton.

DR. DAUM: I presume you have no financial

or commercial involvements --

DR. KAPIKIAN: No.

DR. DAUM: -- in this issue.

DR. KAPIKIAN: The NIH has a CRADA with Wyeth Lederle Laboratories.

Melinda, could you comment on the discrepancy which I believe is a discrepancy actually -- you stated it wasn't -- in the CDC data regarding the attributable risk in the case control study which from your data is really one in 4,500, with the 888 excess cases; with the attributable risk reported recently by the CDC in the ten managed care organizations, which included several hundred thousand individuals as you know, which reported an attributable risk of one in 12,274 doses.

To answer the question the gentleman there asked, in people there was a triple risk of one in 12,000 individuals in the ten managed care organizations, and whereas in the case control study it included only about 2,000 individuals as you stated, 400 cases, and about 1,600 non-cases.

Whereas in the study reported by CDC, there were six cases of intussusception in 61,000 individuals who were vaccinated. That wasn't attributable risk. That was six cases in the first

three weeks after 61,000 individuals, and the attributable risk was calculated by CDC to be one in 12,000.

Now, one in 12,000 is 60 percent less than the figure that you have reported and that CDC has reported previously. It's our feeling very strongly that the attributable risk from a cohort study that includes 60,000 individuals gives us a much greater confidence in what the risk of this vaccine actually is.

And we feel also that decisions that are made by committees like today here and by the ACIP would be modified perhaps or would be at least discussed in a different vein with an attributable risk of one in 12,000.

And of course, those figures are still being analyzed, and we've asked as you know, as Dr. Snider knows, I've asked at the WHO meeting in Geneva what we need to know is what happens after the cases are studied for a comparable period of time with the controls. Is this a triggering effect? Does intussusception decrease later on? If rotavirus, indeed, is associated with intussusception, what happens later on?

So that if we get a person-year

calculation that includes a year's follow-up for the cases and for the controls, we wondered if the attributable risk from this vaccine will disappear totally. Right now it's one in 12,000, and it's really quite different than what you presented, which came out to be one in 4,500 with your 888 figure.

I'd like your comment on this discrepancy.

DR. WHARTON: Well, obviously both of these --

DR. DAUM: Thank you, Dr. Kapikian.

We will allow a single comment.

DR. WHARTON: These are -- both of these are preliminary analyses, and final analyses of both of these studies are still ongoing.

As far as the question about the chance that this is a trigger, clearly that does require long term follow-up, and that's not feasible within the design as the case control study that is being undertaken in the retrospective cohort study done in managed care, and that is the way in which we will be able to look at that issue.

DR. DAUM: Thank you, Dr. Wharton.

I'm going to stop this now. It's an open public session and invite further comment.

DR. MORENS: Thank you.

Is this microphone on or not? Yes.

I'm David Morens from NIH, and I have no commercial or financial conflict or interest.

My comment really is related to the risk-benefit discussions that have been going on, and as I was listening to the discussion I was doing some arithmetic, and granted the figures that are used are open to question, but I had also heard as Dr. Kapikian had the more recent CDC figures that I think CDC claims are the ones they're going with, one case per 12,274 vaccinated kids.

And if you compare that with Dr. Shiels' presentation in which he, I believe, showed that the mortality from intussusception is less than .5 percent, and if you also calculate four million kids born in the United States every year, I think my arithmetic says that even if the association is true and of the magnitude that CDC suggests, that would be one excess case of vaccine associated death per year compared to perhaps 20 or 40 lives saved from the vaccine if it were licensed.

So I guess to me that sounds like an order of magnitude difference such that I just question why the vaccine is not on the market now, why it isn't being used. I think the data that we've heard from

CDC, while they're troubling, are far from confirmatory. These are basically fairly dirty screening data, but all the figures that I look at that I've seen presented by CDC and by FDA suggest that the risk-benefit analysis is greatly in favor of the vaccine.

DR. DAUM: Dr. Morens, thank you very much for your comment.

Are there other comments for the open public portion of this morning's meeting or early afternoon's meeting?

(No response.)

DR. DAUM: Okay. Well, we will use the remainder of our morning session to invite committee members to free associate, if you will, on the information that they've heard and to perhaps reflect is the right word on what they believe we've learned this morning and from the experience that we've had about the prevention of rotavirus disease by vaccination.

Dr. Huang.

Dr. Kim.

DR. KIM: I would simply just like to add one more item to be included into research areas for the future to understand the pathogenicity. You know

that genomic data is coming out and is rapidly expanding. Perhaps that can be included in cases versus controls of rotavirus, particularly associated with intussusception to see whether there is any host factors that contribute to such complications.

DR. DAUM: Other comments?

DR. FOST: This might be anticipating this afternoon's discussion.

DR. DAUM: Well, we don't want you to anticipate this afternoon's discussion. So if there are specifically items related to what you believe will be discussed this afternoon, we'd like to defer that.

We'd like general comments though about vaccine development in this area.

Dr. Snider.

DR. SNIDER: I'd like to make a general comment about risk and benefits, to not defend any particular estimates at this point in time because, as Dr. Wharton has said, the analytic work is ongoing, and I'm not privy to what the specific numbers are, but I think it is important, and in one of the things that was considered by people who had to grapple with the decision last year is the fact that rotavirus vaccine and complications is not done in isolation,

but in the context of an entire immunization program, and therefore, risk of vaccines of any sort, such as oral polio vaccine, which is another issue we grappled with, have to be done in the context of trying to understand how the public perceives risks and benefits of vaccines and the context in which they are administered in the United States and not just a single -- it's not just a simple calculation of one vaccine risk-benefit for that single vaccine, but it's in the context of the acceptability of the entire immunization program.

And I think that's something important to keep in mind for each of the vaccines we consider in this committee, not just rotavirus.

DR. DAUM: Thank you, Dr. Snider.

Perhaps -- well, let me call on your first, and then try and stimulate some more discussion here.

DR. FOST: Thank you.

Dr. Snider's comment, I think, gives me permission to comment, to say it in a different way. I think it's a trap to discuss clinical trials of rotavirus vaccine or a policy of the administration as an all or none phenomenon. It is either it should be distributed or it shouldn't or a trial should be done

or it shouldn't.

It will vary enormously depending on where it is done. That is, doing a malaria vaccine trial in Idaho would not be very sensible, but it might be very sensible in a country where people are dying at a high incidence from malaria.

Similarly, with regard to the trial that are under consideration as well as past trials, it might make much more sense to do this trial in a place where the morbidity and mortality from rotavirus is much higher than it is in the United States, and even within the United States, a trial, as my college Baruch says, in downtown Houston might make more sense than in Madison, Wisconsin, where the burden of rotavirus vaccine is minimal to negligible, or rotavirus diseases is negligible.

So questions of trial design, of where to conduct -- say you had a given trial design. It might make a lot of sense, that is, the benefit-risk ratio of such a trial might be very favorable in a developing country and not at all in a middle class suburban U.S. center, and the same comment would be true for the licensing or at least the clinical use of the vaccine. It might make very good sense to use this in certain areas in this country and others and

not in affluent areas where the disease burden is low.

So I think it's a mistake to discuss this as should we or should we not have a trial or should we or should we not license any of these vaccines.

DR. SNIDER: If I could just add a piece of information because I think that's an important point, the WHO ethics work group made the recommendation along the lines that you propose, but in fact, they suggested that we do simultaneous studies in the kinds of populations in the U.S. you were talking about or in developed countries and in developing countries, and that these be done simultaneously and we not do them in sequence or leave the developing countries out.

DR. DAUM: Ms. Fisher, then Dr. Kohl.

MS. FISHER: Well, I appreciate Dr. Snider's comments, and in that context, I'd like to add that I heard from a number of parents whose children had intussusception following rotavirus vaccine, and I can tell you that those parents were extremely upset when they looked at the benefit risk ratio to their child in terms of rotavirus being for most children in this country not a disease that ends in death or injury.

Intussusception, as Dr. Shiels knows, is

not an innocuous complication for a number of children, particularly if surgery is involved, and parents look at the benefit-risk ratio for their child, and it is very different for rotavirus than it is for smallpox, polio, diphtheria or some of the other vaccines that we use.

DR. DAUM: Dr. Kohl.

DR. KOHL: I want to reiterate what Melinda touched on. In the year 2000, I don't feel like I, and maybe we, have a real good handle on exactly who gets rotavirus in this country, exactly how many kids are hospitalized right now in this country, and in particular, who's dying from rotavirus in this country, and indeed, is anyone dying from rotavirus?

There are probably some, a real teeny number, it's hard to get a handle on that, number one.

Number two, the question about using rotavirus in other countries, vaccine in other countries brings up the interesting economic consideration that companies go through. They can't sell a vaccine for 60 or 80 or $120 in Africa where the annual budget for health care is $10 a person or less.

So we may pontificate about that, but the

hopes of that being used worldwide is not great.

DR. DAUM: Can I ask the committee or paraphrase a couple of thoughts from Dr. Carbone's presentation about issues that the FDA would like to hear us reflect on a little bit?

And that is that if you had a safety database from small preliminary trials, how would that allow you to think about advancing to a larger trial?

And also, how would you go about designing a trial so as to be pleased that intussusception was unlikely to be a problem when a new rotavirus vaccine was deployed?

So I'm going to call on Dr. Brody first because he had his hand up, but please give some thought to these questions because FDA would like to hear our thoughts about them.

DR. BRODY: I actually hope to address that question as well.

I'd like to make just quickly three observations. One is it's extremely important in the assessment of risks and benefits to distinguish ex ante and ex post. When there's a small chance of a troublesome thing, ex ante that looks like a reasonable bet. Ex post if you're one of the few cases, it looks very bad.

Consequently, testimonies from those few people who are ex post victims are the ones that have to be heard, but on the other hand, they hardly are definitive in settling the issues.

The second point I wanted to make was about the economics. I think it's a very serious issue. I share with you the view that if, in fact, there's no reason to suppose the vaccine is likely to be available afterwards in the countries in which you test them, it would be inappropriate to run the trials for them in those countries, and in fact, that's the view that has widely emerged in another area which I'm much involved in, namely, the testing of AIDS drugs.

I don't think we want in this area to get into the same terrible fights that arose with Third World trials in that question.

But the third is on this question you raise of the FDA's request for advice. I think one of the crucial things, and I think it's very important in response to the remark that was made earlier, is that when we think about what would be an appropriate safety endpoint for evaluations and trials, we need to think long and hard about this risk-benefit ratio, and it isn't just a question of the number of cases of intussusception. It's a question of what are the

health implications of those numbers of cases of intussusception, and that may have a big impact upon thinking about whether some suppositions of excess risk being inappropriate may be excessive and may be too conservative.

DR. DAUM: Thank you.

Can we have further committee comment on these issues? How would we go about designing such a trial? How big would it have to be? What preliminary data would we like to see?

Maybe we'll just go down the table. Dr. Stephens, could we ask for a comment?

DR. STEPHENS: It's always dangerous to sit at the end of the table.

(Laughter.)

DR. STEPHENS: I think at least my perception of the discussion this morning, I'm still in need, if you will, of more data concerning the pathogenesis of intussusception. I'm intrigued by the potential of animal studies that may be available to look at intussusception as a risk factor.

However, I think it is important to emphasize what already has been said, and that has to do with the risk-benefit ratio and where you're going to study this particular vaccine.

Obviously in the developing world, rotavirus is an important disease and one where a vaccine is clearly needed. The issues in this country are somewhat less clear. I would want to see a study of this vaccine in the developing setting, in my opinion, maybe in contrast to looking at this vaccine in the developed world.

So I think the risk-benefit ratio is an important one in the study and design of trials of where this vaccine is going to be used.

DR. DAUM: Thank you.

Dr. Huang, could we hear your views on this?

DR. HUANG: Not being a clinician, I'm going to not have all that much to say about the design of clinical trials, although I am very intrigued by the findings of lymphoid follicles and their relationship to the side effects, and it causes one to wonder whether even when we're thinking about efficacy, whether the development of the infant in terms of immune responses would really play a role, and I think that obviously that calls for more studies to be done.

I would hate to see the fact that we don't make vaccines that would be helpful to developing

countries just because we think that they will become too expensive for those countries. I think that where vaccines are truly needed, and certainly in the rotavirus infection case it is the developing country that needs it, and in our discussions of this, that we ought to really take that into consideration.

And I certainly second the suggestion that if I were designing a clinical trial, I would like it to be done in those places where the vaccine would be most needed.

DR. DAUM: Dr. Snider, please.

DR. SNIDER: Well, just following on what has recently been said, I think this is a very problematic issue with regard to trying to do an assessment of benefits and risk because as has been pointed out, the ethics of conducting a good clinical trial, indeed, even the scientific requirements of doing a good clinical trial, impact on the risks and benefits that will be observed.

In other words, as was mentioned earlier, when you try to study this even in a developing country, you wind up providing levels of clinical care to the population even to the control population that is not necessarily received by those who need the vaccine most, who don't have access to oral

rehydration therapy or intravenous therapy.

So that you wind up in this dilemma of wanting to have a vaccine most for a population in whom the risk and benefits become almost impossible to define because they won't be in places where there are tertiary care centers where you can do this kind of trial ethically, and they won't have -- even if they are in those places, they'll have a different standard of care during the trial likely than what would ordinarily be the case.

So I hate to, you know, keep waxing philosophical about this rather than getting to some of the scientific issues, but I think it's extremely -- I mean, these are some of the difficult problems that impact on the answers to the scientific questions, such as, you know, how large does the trial need to be.

I mean, obviously we need to have a large enough population that we're likely to be able to detect an excess risk that's in the ranges that have been calculated, but in order to be able to do that, there's going to be large sample sizes required, and the results that come out of the trial like that won't necessarily be relevant for the kids who really need this vaccine the most who are not going to have access

to or have access to very little or no medical care.

DR. DAUM: Dr. Griffin, could we hear your thoughts about this?

DR. GRIFFIN: Well, I'm not a statistician or clinical trial designer so that I can't really comment, except that it seems like we would be greatly helped if we understood the pathogenesis more. Most everybody would agree to that.

But one of the reasons that we might be is, first of all, we're dealing with very low frequency events, but presumably this is a spectrum of problem many of which have some precursor to intussusception that doesn't go on to intussusception, in addition to the patients who may spontaneously reduce their intussusception.

And if we could have some way of marking whatever that -- whether it's a motility change or if it's a change in lymphoid tissue or something where you could genuinely look at the precursors that would predict that some percentage of those kids are most likely to get intussusception, I mean, as Dixie just said, you need huge sample sizes right now to detect these very infrequent events, and even then, you know, your confidence is not very secure that you're going to be able to identify the events, but I guess if we

had some other way or some other marker or some other surrogate which requires understanding the pathogenesis basically of why the vaccine might be predisposing to this process.

DR. DAUM: We're heard from Dr. Kim a bit. Would you like to comment on this issue? We'd appreciate it.

DR. KIM: Well, again, I think I pretty much echo what everybody has said, that we need more information on the issues related to intussusception particularly following vaccination.

And I'd like to see the completion of data analysis being currently going on in CDC with respect to the different numbers being, you know, discussed, and again, I think that would be beneficial in designing clinical trials, that what is the end that will be required to meet the objective study criteria.

DR. DAUM: Ms. Fisher, did you want to comment on these issues of how to know how to go forward?

MS. FISHER: Yes. I think that in a design of a clinical trial on a rotavirus vaccine, it's going to very much depend upon what that rotavirus vaccine is, and if you're talking about, for example, the genetically reassorted human and animal

viral vaccines, I think that you have to look beyond intussusception, and it becomes extremely important. Pathogenesis becomes extremely important with regard to potential chromosomal change, residual RNA, DNA and that sort of thing.

And so I think that you really have to look at what vaccine you're talking about before you can with confidence go forward with a clinical trial.

But I think there are certainly genetic issues, whether you're going to use this vaccine in combination with other vaccines and whether you're going to be vaccinating sick children. That sort of it is very important.

DR. DAUM: We're getting to the point where we need to stop. Dr. Atreya and the pathogenesis summary that he presented this morning, you're hearing a plea for you to go faster, marshal the troops, do more, do it quickly.

We're also hearing, I think, a clear statement that there's a lot of death and morbidity in developing countries from rotavirus infections, and we may not have the perfect vaccine that we like, but we have to weigh the risks and benefits of using them and testing them against death of many, many children.

We also have, I think, perhaps discounted

a little bit the impact of disease in our own country. Certainly the inner city tertiary care institution that I work in has lots of kids hospitalized every winter with rotavirus, lots of nosocomial rotavirus cases, and although I am sympathetic, of course, to parents who believe they were injured, whose children were injured by this vaccine, I'm also sympathetic to parents whose children are injured, if you will, by the wild type virus and get sick, get hospitalized, need IVs, need therapy, and the complications of hospitalization and those therapies.

So I think we've got some imperfect and very difficult issues to grapple with here. In the meantime we encourage the science to go forward as fast as it can, but that doesn't get us off the hook of considering these very hard public health, ethical, moral, and scientific issues.

And with that, it's lunchtime. Unlike the real Chairman of this committee, I believe in lunch, and so we're going to have a hour lunch.

DR. FLEMING: Mr. Chairman, did you not want any statistical or ethical input into this question?

DR. DAUM: You know, I'd love it. Can I finish this lunch comment? And then we'll have your

comment and then we'll adjourn.

One second.

DR. FLEMING: Just mine?

DR. DAUM: Well, I felt like we've heard from this side of the table. If there are comments, Dr. Fleming, please. We are dying to hear from this side of the table. Please excuse me.

Dr. Fleming, please, and Dr. Verter and others that wish to comment on these issues. Dr. Fleming.

DR. FLEMING: You did want comment?

DR. DAUM: Very strongly.

DR. FLEMING: It didn't sound like it.

DR. DAUM: I apologize for not sounding like it.

DR. FLEMING: I think this is a very important issue, and I'd like to provide some statistical perspectives on what would be the background information we would need in a difficult situation like this.

My sense is that we need important clues about plausibility of whether we have a favorable benefit to risk profile, and certainly this is complex, as we've heard, in that these issues of benefit to risk can certainly depend on population,

and we may well intentionally attempt to target the confirmatory trial to a population where it is most likely to have a favorable benefit to risk.

Nevertheless, I would say it's going to be important when we do the studies, preliminary studies and phase three confirmatory trials, to do so in populations that allow us the ability to generalized conclusions to broader settings in which these issues will be important.

My sense of what we would need to look at in settings like this, certainly we look for clues about efficacy as well as safety, and from the efficacy perspective, we have often needed to focus on immunogenicity issues. In this setting though it's certainly going to be possible to get important clues about efficacy on direct measures, such as moderate to severe or especially severe RV disease, hospital admissions, health care use.

How plausible is it for a vaccine based on these types of data to expect benefit that could then be confirmed in phase three trial?

From a safety perspective it's going to be impossible to expect to get data on rare events, but what we certainly can get is information on common AEs, fevers, injection site reactions, et cetera, and

biological insights about the plausibility of risk for rare but profound events will be very key to consider.

Ultimately though a phase three is going to have to be where we would get into issues of rare events, and typically we don't always require that the phase three trial identify conclusively what are the ultimate rare event risks. We often rely on what might be post marketing phase four, active or passive surveillance.

But in a setting such as this where there is obvious and significant expectation that these risks are real, then it is important for the phase three trial then to be designed to address those issues, and as we'll see this afternoon, those could require sample sizes on the order of 60 to 100,000.

DR. DAUM: Thank you.

Are there other members from this side of the table inadvertently excluded from commenting? Dr. Shiels.

DR. SHIELS: Very briefly.

DR. DAUM: We won't delay lunch too long.

DR. SHIELS: Two issues, pathogenesis and the clinical trial suggestions.

Pathogenesis, one thing that we do know that adds to our understanding of pathogenesis as far

as motility, this is after the intussusception has occurred. We do know that once we reduce the intussusception that there is no reason to believe that there is a motility disturbance present.

Let me repeat that. Once we reduce the intussusception, there's no reason to believe that there is a motility disturbance in these children. The reason we know that convincingly is because we are sending these children out of our hospital as out patients. A large number of our children do not ever see the hospital, except the radiology suite. They have their intussusceptions reduced, and then they go home, and they eat right way, and they're not having recurrence or revisitation of the hospital because of a motility disturbance.

So there is good reason to believe that it's not primarily a longstanding motility disturbance.

As far as study design, two suggestions. Number one, as far as diagnostic studies, I think we need to be very clear on the significant limitations of plain X-rays. If we're going to surveil children and observe them with accurate diagnostic studies, we need to target ultrasound for the pre-therapeutic evaluation of children, for the definitive diagnosis.

That has to be clearly targeted. The next follow-on to that is the ultrasound done in children is not done universally well by all radiologists. It's a very important point. If there's any one imaging modality that takes artistry, commitment, compulsion, and expertise, it is ultrasound.

Ultrasound in children, if it's going to be in the setting of surveillance, should be focused, if at all possible, if at all possible, in centers where the community cachement area has effective focus of their pediatric expertise, a three part team, pediatric medical specialist, pediatric surgeons, and pediatric radiologists.

There's a good list of roughly 13 major urban centers where this country can count on urban center populations with good trial data in children that live in high density populations, good focus care of pediatric teams, including reliable pediatric radiology at any time of the day or night, and that's the other point.

We don't delay diagnosis until eight o'clock in the morning when some radiologists come to work. We need to be able to count on radiologists doing these studies at two in the morning or one in the morning, and there's a good list of roughly 13

centers that have good community focus of their care at children's hospital centers of excellence, and not all large cities have that.

DR. DAUM: Thank you, Dr. Shiels.

The official FDA timepiece indicates that it's 1:08 here in the Eastern time zone, those of us that are disoriented, and we will take exactly one hour for lunch and convene at 2:05 with a closed session.

Our consultants are all included in the closed session, and we'll see you all then.

(Whereupon, at 1:05 p.m., the open session was concluded, to reconvene at 2:05 p.m., the same day, in closed session.)

CERTIFICATE

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

Before: DHHS/FDA/PHS/CBER

Date: May 11, 2000

Place: Silver Spring, MD

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