to eight degrees Centigrade.

The proposed indication and usage, prevention of rotavirus gastroenteritis in infants and children caused by those serotypes. Administered as a three dose series with the first dose given to healthy infants at six to 12 weeks of age, followed by two additional doses administered at the four to ten week intervals.

The regulatory history for RotaTeq, which Dr. Heaton has already outlined, in June of 1993 the Phase 1 study 001 was initiated. In August of 1998, RotaShield was approved. In July of 1999, RotaShield was withdrawn. In May of 2000, the AC meeting, the Advisory Committee meeting, was held to discuss the design of REST.

In January of 2001, study 006, which is the REST trial, was initiated. In November of 2003, the 60,000th subject was randomized to REST, and in September of 2004, the 70,000th subject was enrolled in REST.

In November of 2004, the DSMB recommended stopping the REST enrollment because they felt that

the primary safety hypothesis had been realized, and in April of 2005, the BLA was submitted to the FDA.

Clinical studies, again, the Phase 1 and 2 trials were studies 001 through 005. There were 2,470 infants and 30 adult subjects.

The Phase 3 study, the number of subjects vaccinated you can see. In the RotaTeq and the placebo arms, study 006, again over 70,000 children. Study 007, 650 and 660 in those study arms. Study 009 -- I'm sorry. Study 007 was the end expiry, and Study 009 is the lot consistency trial with 679 in the RotaTeq arm and 112 in the placebo arm.

The Phase 3 studies, the demographics, across the treatment arms; gender, approximately 50 percent male and 50 percent female; race, about 69 percent white. The subjects that participated were from the following countries, and that included about 48 percent U.S. and Puerto Rico: 33 percent, Finland; 19 percent, Costa Rica, Guatemala, Mexico, Jamaica, Taiwan, Belgium, Italy, Germany, and Sweden.

About 90 percent of the trial was done at a U.S. IND.

The Phase 3 inclusion criteria that I'm going to note here, the healthy infants age six weeks through 12 weeks of age; healthy premature infants who were less than or equal to 36 weeks of age, and they were enrolled according to their chronological age. There were no restrictions on breast feeding, and there were no restrictions on concomitant vaccines, except that oral polio vaccine was not allowed.

Phase 3 exclusion criteria, this is not all of them, just the ones we wanted to highlight. Rectal temperature, greater than 38.1; any history of congenital abdominal disorder; history of intussecption or abdominal surgery; history of immune deficiency; history of living in a household with an immunocompromised person; chronic diarrhea; history of rotavirus disease; receipt of blood products, immunoglobulins, or immunosuppressive therapy; and again, receipt of OPV.

The important cohorts to keep in mind in the Phase 3 studies, the large safety cohort, again, over 70,000 children in studies 006,007, and 009. The detailed safety cohort, which enrolled about 11,753

children, that contained a subset of study 006 subjects, and then it contained all the subjects in studies 007 and 009.

And the U.S. concomitant use cohort contained 1,358 children. That was a subset of the efficacy cohort.

The efficacy, the case definition, three or more watery or looser than normal stools within a 24 hour period and/or the forceful vomiting, and then the rotavirus antigen detected by enzyme immunoassay in the stool specimen taken within 14 days of symptom onset.

For the primary efficacy analysis, on the G1, G2, G3 or G4 specific rotavirus gastroenteritis cases, naturally occurring through the first full rotavirus season that began at least 14 days after the third dose of RotaTeq or placebo were included.

For study 006, this was the REST trial. It was a Phase 3, double blinded, randomized, placebo controlled, international, multi-center study to evaluate the efficacy, immunogenicity and safety of RotaTeq.

The primary objectives of study 006, to evaluate the efficacy of the three dose regimen of RotaTeq against rotavirus gastroenteritis caused by the serotypes G1, G2, G3, and G4, again, occurring at least 14 days following the third vaccination, and then to evaluate the safety of RotaTeq with respect to intussecption with 42 days following any vaccination.

Study 006 efficacy. The primary null hypothesis was the efficacy of RotaTeq against all G1, G2, G3, and G4 specific cases of rotavirus gastroenteritis that, again, occurred through the first rotavirus season that began 14 or more days post dose three and would be less than or equal to 35 percent.

The efficacy for the FDA, we just finished this yesterday. Our statisticians worked with the raw data. This is my favorite slide.

In any event, for study 006 -- and we separated out the studies because the null hypothesis is different -- but for study 006, the subjects vaccinated, again, 2,834 for RotaTeq; placebo, 2,839. The subjects in the efficacy analysis, 2,207; and the

placebo, 2,305.

The days of follow-up and the way the cases are ascertained are still a little bit different between the FDA's way of methodology and Merck's, and this application is still under review. So we're still working on this, and our statistician can give you an explanation of where we're at with this.

But the bottom line is that the efficacy estimates are extremely similar with 73.9 for the FDA and Merck 74. So, again, we're very, very satisfied at where we're at, and again, our statistician can go into this in a little bit more detail since we just finished with this.

That's for study 006. Again, study 007 is the end expiry. This is the Phase 3, double blinded, randomized, placebo controlled study to evaluate the efficacy of RotaTeq at end expiry. Again, the primary objectives, to evaluate the efficacy of the three dose regimen of RotaTeq at expiry potency against naturally occurring rotavirus disease caused by the composite of the serotypes contained within the vaccine, G1, G2, G3, and G4, again, occurring at least 14 days after

the third dose.

The primary null hypothesis, different for this study; the efficacy of RotaTeq at expiry potency against all G1, G2, G3 or G4 specific cases of rotavirus gastroenteritis, again, occurring at least 14 days after dose three through one rotavirus season would be less than or equal to zero percent.

So we don't lump the data together. We like to show you the efficacy of the studies separately.

And again, for study 007, for RotaTeq the subjects vaccinated, 650; for placebo, 660. You can see the number of subjects in the efficacy analysis: RotaTeq, 551; placebo, 564. Again, you can see the days of follow-up and the way the cases are calculated is slightly different, but the bottom line, the efficacy estimates on the 95 percent confidence interval, 71.9 for RotaTeq; 47.1 to 86.1 for the FDA; and, again, for Merck, 72.5, with the confidence intervals, 50.6, 85.6.

And, again, our statistician is satisfied with these results, but they are continuing to work

with Merck on this.

The safety cohorts, again, the large safety study 006, 007 and 009. Again, over 70,000 infants randomized, and seven days of detailed safety for these children, and they were monitored about every six weeks for serious adverse events, and intussecption to 365 days post vaccine dose one.

For the detailed safety, the subset of study 006, plus the subjects from 007 and 009, comprise the detailed safety. Again, 11,753 infants randomized.

Again, 42 days of detailed safety for these children, both serious adverse events and adverse events, and again monitored every six weeks, out especially for intussecption and serious adverse events out to 365 days post vaccine dose one.

There was a safety endpoint adjudication committee which you've heard about already: three physicians with expertise in pediatric surgery, pediatric radiology, and the clinical diagnosis of intussecption.

The adjudication was blinded to treatment

assignment and used prespecified case definitions and adjudication guidelines. If there was a disagreement, a majority ruling was made. All adjudications were made by the committee and they were final.

Again, the data safety monitoring board, which you've heard about also, experts in operational medical, biostatistical aspects of clinical trials. They were not involved in the conduct of the study, and they considered all SAEs, all serious adverse events, and specifically intussecption cases.

They unblinded the treatment arm of positively adjudicated intussecption cases, and they made recommendations regarding the ongoing conduct of the study.

Primary safety hypothesis. RotaTeq would not increase the risk of intussecption relative to placebo within 42 days of any vaccine dose, and the statistical criteria included distribution of intussecption cases between the vaccine and placebo. The case split would not reach a predefined safety boundary for any of the two overlapping day ranges, one to seven or one to 42 days following any dose, and

this was being monitored by the DSMB, and the upper bound on the 95 percent confidence interval, the estimate of the relative risk of intussecption had to be less than ten.

I want to talk about intussecption. It's the most frequent cause of intestinal obstruction in the first two years of life. It's an uncommon illness with an estimated annual incidence of one out of 2,000 among infants less than two years of age.

The symptoms you've heard about already: irritability, abdominal pain, vomiting, lethargy, blood or mucous containing or current jelly stools, and it can be fatal if it's left untreated.

Cases were confirmed by contrast to enema, ultrasound, surgery, or autopsy, and some cases may spontaneously reduce.

A case of intussecption had to be diagnosed, again, radiographically at surgery or at autopsy in the trial. The intussecption case definition was similar to the Brighton collaborations intussecption working group definition, except that Brighton calls for an initial ultrasound diagnosed

case to be followed up with another ultrasound to demonstrate resolution or reduction of intussecption.

The Merck diagnosis permitted ultrasound cases alone to be included because they didn't want to miss any cases that might spontaneously reduce. So a conservative definition.

Intussecption for the prespecified 42 day post vaccination endpoint. The results demonstrated six cases of intussecption versus five cases of intussecption in the placebo group. The estimated relative risk of 1.2 with a 95 percent confidence interval of 0.3 to five was obtained, and the upper bound of the 95 percent confidence interval of the relative risk is less than ten, which satisfied the prospectively specified primary safety objective of REST.

I want to just go over some of the cases with you if I can. I hope you can follow this diagram, but this shows the spread of the cases according to different windows, zero to seven, zero to 14, zero to 21, zero to 42, and zero to 60, and then zero to 462.

This is all cases of intussecption, and this is, again, looking at it split after vaccine dose one, vaccine dose two, and vaccine dose three. In the zero to seven window, there was one case in the RotaTeq arm, and again, that occurred after vaccine dose number two.

In the zero to 14 window, there was one case in the RotaTeq arm and one case in the placebo arm, and again, the split was there was a case that occurred after dose two for RotaTeq and then for placebo after dose three.

In the zero to 21 window, you can see there are three cases of intussecption for RotaTeq versus one case for placebo, and the three cases for RotaTeq occurred at vaccine dose two, and the one case for placebo again occurred at vaccine dose three.

At zero to 42 days, this was the endpoint. There were six cases of intussecption with RotaTeq to five of placebo, and again, looking at what the spread was, there was one case for placebo that occurred after vaccine dose one, and again, you can see RotaTeq coming in here at that dose number two. There's four

cases here, and then one in the placebo arm that occurred at vaccine dose two.

If you look at vaccine dose three, again, two cases for RotaTeq, three for placebo.

At zero to 60 days, the split was eight cases in the RotaTeq arm to six in the placebo. For vaccine dose one, it was equal, one RotaTeq, one placebo, and again, at vaccine dose number two, there's five cases for RotaTeq, two for placebo. Vaccine dose number three, two RotaTeq to three placebo, and these were the case splits at zero to 462 days, 13 to 19. So more in the placebo arm.

There was also a case of intussecption that occurred in some of the earlier -- actually study 005, an earlier study. That was a dose ranging study, and this case of intussecption occurred in an older child that was a seven month old male who had received a low dose of pentavalent vaccine, and that child developed hematochezia and vomiting, and intussecption was diagnosed at surgery on day nine post dose one.

And at surgery the pathology was benign lymphoid hyperplasia, and we were concerned about

that, and we asked Merck to do an exploratory analysis to add that child into the entire spectrum of intussecption that we had seen in the Phase 3 trials, and they went ahead and did that and found a relative risk of 1.4 and the confidence interval 0.4 to 5.6.

Ultimately, there was no increased risk of intussecption at day 42 post vaccination compared to placebo. There was no clustering of intussecption cases within the early, the seven or 14 day window post vaccination.

We looked at intussecption also to see how many children went to surgical reduction, and again, you can see at zero to 21 days there's one case that went after dose two in the RotaTeq arm, and then there are cases that went after dose three at the 22 to 42 day window and greater than 42 days. Compare that to placebo; those cases all went late, post dose three, greater than 42 days, and that's just to give you an idea of how many cases required surgery.

We were very interested in hematochezia. So we wanted to look at both the positively adjudicated children and the negatively adjudicated

children to see if there were any differences.

For the positively adjudicated cases of intussecption in that zero to 21 day window with the RotaTeq arm, there were three in post dose two, and then when you come down into the next window, the 22 to 42 day window, you can see after post dose two for RotaTeq. There's one case, and then there are two cases post dose three.

Again, you can compare that to placebo. There was one case after post dose two, one case after post dose three, and again, you can see the spread at greater than 42 days. With one case after post dose one for RotaTeq, one case after post dose two, two after the third dose with RotaTeq.

The total number of intussecption cases was 13 that I looked at in this series, and hematochezia occurred in ten in the RotaTeq.

Placebo looked at the 19 cases of intussecption that we had and there were seven episodes of hematochezia in the placebo arm, and again, you can see the spread with those children for the placebo, one after post dose two, one after post

dose three, and the window 22 to 42 days, and then in the greater than 42 day window for placebo, there was one post dose two and four post dose three.

In the negatively adjudicated cases of intussecption, some of these children had hematochezia, and I used the table that Merck provided to show you the spread of the cases of hematochezia with these children, and again, with RotaTeq there were 45 negatively adjudicated cases and ten of those had hematochezia for RotaTeq, and you can see in those days post dose zero to 21 there were five cases for RotaTeq after the first does. There was one after the second and one after the third.

And compare that to placebo. There were two cases after post dose one, again, keeping in mind that the total number of cases of placebo that were negatively adjudicated was 47, and there were three that had hematochezia.

And then, again, in the last window, greater than 42 days for RotaTeq there was one case of hematochezia post dose two, and there were two after the third dose, and then one case of hematochezia for

placebo that occurred after the third dose, and that was greater than 42 days.

This analysis for FDA was a combination of looking at Merck's table and also looking at the narrative summaries at hematochezia, and again, with RotaTeq the total number of negatively adjudicated cases was 45, and there were 17 cases of hematochezia, and again, a lot of early cases of hematochezia, zero to 21 days. After post dose one there were seven; post dose two, three; post dose three, one. And then placebo had four post dose one, and two post dose two, again, keeping in mind for placebo there were 47 negatively adjudicated cases, nine episodes of hematochezia.

At the 22 to 42 day window there was a case post dose two for both RotaTeq and placebo, and then greater than 42 days there were two cases post dose two for RotaTeq, three post dose three, and then placebo had two cases post dose three.

Overall for intussecption the results from the study don't address use in infant populations who were not studied, such as children with HIV or

underlying gastrointestinal disorders or infants who reside in areas outside the U.S. where the standard of care is to give live oral polio vaccines.

And, again, we also have limited data regarding the administration of first dose to infants at an age greater than 12 weeks or administration of a third dose at approximately 34 weeks of age or beyond 34 weeks of age.

Looking at the deaths in the Phase 3 studies, there were no deaths in Phase 1 and 2. There were 52 deaths in the Phase 3 studies. There were 25 in the RotaTeq arm, 27 in the placebo, and again, the most common cause of death was SIDS, with RotaTeq at eight and placebo nine.

There was one death with intussecption in the trials. This was a white male, and it was randomized to the RotaTeq arm, and on day 96 post dose three he developed abdominal pain, vomiting, bloody stools and a barium enema confirmed intussecption.

This subject went to surgery, had necrotic bowel resected, developed septicemia, and died on day 99 post dose three of vaccine, but again, this was a

late case.

We looked at serious adverse events for RotaTeq, again in Phase 1 and Phase 2. The intussecption case I've already described in the study 005. The incidence of serious adverse events in Phase 3 at less than 30 -- I'm sorry -- at less than 42 days, RotaTeq was 2.1 percent versus placebo was 2.2 percent. Discontinuations at less than or equal to 42 days post vaccine dose due to serious adverse events in Phase 3, RotaTeq was 0.23 percent versus placebo at 0.2 percent. So matched.

The most frequent rhesus adverse events in the Phase 3 trials, bronchiolitis, gastroenteritis, pneumonia, pyrexia, and urinary tract infection, and again, you can see this more gastroenteritis in the placebo arm and pretty well balanced with pyrexia with fever.

We looked at seizures in the Phase 3 trials and pulled this out at less than seven days post vaccine dose, less than or equal to 14 days post vaccine dose, and then looked at it at less than or equal to 42 days post vaccine dose.

And looking at the split at less than or equal to seven days post vaccine dose, it was ten in the RotaTeq arm and five in the placebo arm, and then, again, looking at the next window at less than or equal to 14 days post vaccine dose, the split was 15 in the RotaTeq arm and eight in the placebo arm.

And then when you come out at less than or equal to 42 days post vaccine dose, 33 in the RotaTeq arm and 24 in the placebo arm, and I've also included where they occur post dose as well.

This was a concern also of the DSMB, and they had asked Merck to do an analysis, I believe, that was done before the study was unblinded. So the staff at Merck might want to say a little bit more about the seizures.

There were also children that were allowed in the trial with a history of seizure, but none of those children developed any of the seizures that I've reported here to you.

It's very difficult to evaluate the seizures also. There were not a lot of febrile seizures because a lot of the children in the trial

were actually younger. I believe febrile seizures occurred in a little bit older age, like five or six months of age or greater.

So, again, just difficult. We're not sure if this is a signal, but we did feel that it needed to be mentioned and perhaps we could get some feedback from the Advisory Committee on that.

We looked at hematochezia again, just looking at the Phase 3 subjects and again looked at hematochezia less than or equal to seven days post vaccine dose, less than or equal to 14 days; looked at the less than or equal to 21 days post vaccine dose and also at less than or equal to 42 days, and again, the splits you can see, 13 for RotaTeq versus 21 for placebo; 29 versus 30; 40 versus 33; 45 versus 39.

We also looked at hospitalizations at less than or equal to seven days post vaccine dose, and again, we were just concerned that perhaps children might be having fevers or having vomiting or diarrhea that would warrant their coming into the hospital to be admitted within that first seven days after vaccine dose.

And, again, after post dose one you can see 133 in the RotaTeq arm versus 114 in the placebo arm. Post dose two, 66 for RotaTeq, then more in the placebo arm at 81. And then post dose three, 40 in the RotaTeq arm, 53 in the placebo arm, and the totals, 239 versus 48.

Look at the most common reasons for hospitalization at less than or equal to seven days after any vaccine dose. And again, with bronchiolitis you can see the cases there, 54 for RotaTeq, 59 for placebo. Looked at gastroenteritis, 18 and 25 for placebo. Some more gastroenteritis.

Pyrexia, eight for the RotaTeq arm, 15 for placebo.

Urinary tract infection, more in the RotaTeq arm, nine for placebo.

And pneumonia, 11 for RotaTeq and 14 for placebo.

For solicited adverse events, this is the detailed safety cohort. We looked at this at less than or equal to seven days, and again, for fever for RotaTeq about 12.8 percent versus placebo 11.6

percent. For irritability, 8.1 percent in the RotaTeq arm versus 7.9 percent in the placebo arm. For diarrhea, 11 percent in the RotaTeq arm versus ten percent in the placebo, and for vomiting 6.9 in the RotaTeq arm versus 5.7 in the placebo.

And finally for concomitant vaccines, all the subjects in Phase 3 were permitted to receive licensed pediatric vaccines on the same day or within 42 days of vaccination. They looked at the subset of 1,358 infants, 662 in the RotaTeq and 696 in placebo, and they received concomitant COMVAX, INFANTRIX, HIPOL and PREVNAR, and they were evaluated for immune responses.

The responses were measured at age seven to nine months after three doses of vaccine, diphtheria, tetanus, pertussis and the pneumococcal serotypes at that age, and then responses were measured at age five to six months after two doses of vaccine for Hepatitis B and polio.

And these are the criteria for the antigens: polio, Hepatitis B surface antigen, PRP, diphtheria and tetanus. The comparison is

seroprotection rate, placebo minus RotaTeq, and the standard noninferiority; the upper limit of the two-sided confidence interval for the difference, less than ten percent.

And then again for the Pertactin, the FHA, pertussis toxin, the pneumococcal serotypes, the GMT ratio, RotaTeq to placebo. We used the lower end of the two sided confidence interval for a ratio greater than 0.5.

For the concomitant vaccines, the noninferiority criteria for RotaTeq versus placebo were met for all of the antigens. Except the problem for tetanus, diphtheria and the pertussis antigens is that the assays haven't been validated. And, again, assay validation is under review for the anti-FHA, the PT, the PRN, the tetanus and diphtheria.

And just to summarize, there was no increased risk of intussecption at day 42 post vaccination when compared to placebo. The clinical study data is really not sufficient to support administration of a first dose at an age less than six weeks or a third dose beyond approximately 34 weeks.

We also would need more information about using this product in immunosuppressed patients.

And then we're unable to rule out interference of immune responses when RotaTeq is co-administered with the childhood vaccines to prevent pertussis and diphtheria-tetanus because we don't know. The assays aren't validated yet.

I'd be glad to take any questions from anyone.

CHAIRMAN OVERTURF: We have time for a couple of short questions. Dr. Farley.

Why don't you go ahead and ask your question, Dr. Farley, but we can't hear at all.

DR. FARLEY: The question is in terms of the exclusion criteria obviously this would be a design at a time when RotaShield issues have emerged. Is there any significant difference between who were allowed to go through the RotaShield trials, as well as those with contraindications for use in the RotaShield vaccine, versus who you allowed here, the oral polio vaccine issues. That was still a time it was still in general use.

DR. TIERNAN: Yes.

DR. FARLEY: So could that be impacting our ability to screen out those who might be at risk to the vaccine?

DR. TIERNAN: Yes, the oral polio definitely may be an issue. That would be the big difference. I don't know about the other exclusion criteria. I didn't go back to the RotaShield trials to see what their exclusion criteria were.

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

DR. TIERNAN: I did not go back to look at that either with the RotaShield.

CHAIRMAN OVERTURF: Just to clarify, you said you're not sure whether oral polio or age were exclusion factors specifically for the RotaShield?

DR. TIERNAN: No, I don't know if they were exclusion factors, but certainly oral polio was being used at that time and it was looked at as a concomitant vaccine.

Yes.

CHAIRMAN OVERTURF: We're going to have to

stop until the microphone is on so that we can get this on transcripts.

Are there questions from this side of the table?

(Laughter.)

DR. KARRON: I actually wanted to focus on the issue of seizures that was raise, and I was wondering if we could either get more information from the FDA or from the sponsor about the nature of these seizures, the outcome in the children, those sorts of things, perhaps some of the information that was discussed with the DSMB.

DR. TIERNAN: Yeah, I don't know, Penny, if you -- I think Michelle Govay had some information about the seizure splits.

DR. HEATON: Yes. We looked at all of the seizures that occurred in the study, of course, very carefully, and let me get that data for you.

So is it possible to have our slides up on the screen?

Okay. So the question is about seizures, and first of all, we looked at seizures that were

reported as serious adverse events in the study, and so if I could have Slide 169, please.

Overall there were 41 cases of convulsions. In our analysis, this included any term of seizure, epilepsy, and we also included febrile convulsions as well, and so the total number ended up being 41 with 25 in the vaccine group and 16 in the placebo group for a difference of .02 percent.

For febrile convulsions that were reported as serious adverse events, there were five in each group, and certainly these reports of convulsions and seizures weren't unexpected, given the age of infants in the study. We all know that the incident of new onset seizure is highest in the first year of life, and the overall incidence was within the range that we expected based on published data.

So we also wanted to look at where, you know, most of these seizures clustering after dose one or after dose two or after dose three, and actually a similar proportion of seizures occurred after each of the three doses.

If I could have Slide 172, I can show you

that now.

So we had exactly the same case split for seizures after dose one, 13 cases. Again, these are SAEs, with eight in the vaccine group, five in the placebo group after dose one; the same after dose two, and then after dose three it was 15 with nine in the vaccine group and six in the placebo group.

We also looked at the proportion of cases that occurred within 14 days after a dose. We had 17 overall, with 13 in the vaccine group and four in the placebo group, and you can see the case splits there with, again, the same proportions of cases occurring after dose one, dose two, and dose three.

So it's a little tedious, but it's probably worthwhile to go into some information about these cases. So on Slide 173.

So we wanted to look at those 17 cases within the first two weeks after a dose, and so this is an outline of some of the detail of these cases, and so we had two cases that were febrile seizures. One occurred in the vaccine group and one in the placebo group. The one in the vaccine group had a

typical pneumonia. The one in the placebo group had a UTI.

We had four cases that occurred because of underlying defined structural abnormalities, three in the vaccine group and one in the placebo group. One child had hydrocephalus. One child had brain stem edema secondary to a cardiovascular incident. One child had a permanent arachnoid space that was noted on his CT and MRI, and another child actually had episodes of laryngospasm that was causing hypoxia and seizures.

There was one case that was a little bit unusual in that it was really a startled episode that the mother reported she had had a similar episode to that two weeks before the dose, and then the second episode which was diagnosed as a seizure happened immediately after she received the second dose. I mean right there in the doctor's office.

And so that leaves us with ten cases total who were clinically diagnosed. So what I mean by that is they either had a normal EEG or they did not have an EEG, and you can see here that these are heavily

weighted toward the vaccine group with eight in the vaccine group and two in the placebo group.

Two of these kids in the vaccine group went on to develop defined seizure disorder, epilepsy. There were three kids out of this group that in reading their history they actually had history and evidence of or episodes that were suspicious for seizures before the actual incident that was reported as a serious adverse event.

Two children both in the vaccine group had seizures that were not witnesses by medical personnel, but they did have a positive family history of seizures and the story was convincing. One had acute onset bronchial pneumonia actually that evening, developed positive chest X-ray and had acute onset bronchial pneumonia that was diagnosed shortly after the seizure onset.

Then we had one each in the vaccine and placebo group who had seizures not witnessed by medical personnel, and the history was very questionable as to whether they actually had a seizure, and then finally we had a child in the

placebo group who had clearly defined seizures, but the EEG was normal, and there was no recurrence of the seizures.

So this is a lot of detail about each of the cases, but clearly we wanted to look at these. They are of concern, and you know, I think what we can say is we don't see evidence of a signal of an association with the vaccine. We'll continue to monitor all adverse events though in post licensure setting.

CHAIRMAN OVERTURF: Dr. Royal.

DR. ROYAL: Just to ask a bit more about the procedure, did you limit your seizure diagnosis to just convulsive episodes? Were there reports of nonconvulsive attach seizures?

DR. HEATON: This particular analysis included convulsive-like episodes, be they febrile, afebrile, or also febrile convulsions or diagnosis of epilepsy. There were other things that were certainly reported like infantile spasms, which were similar in the vaccine and placebo group. We had a few cases of that.

Is there a specific diagnosis that you had questions about?

DR. ROYAL: Well, you know, Epson's type episodes and anything that might not be considered a convulsive episode or a focal type episode would certainly be of interest.

DR. HEATON: Right. This analysis actually did include like focal seizures and focal abnormalities as well. The way the mapping of the encoded terms happened, those kids who might have had focal episodes were included in this.

DR. ROYAL: In the structural abnormalities that were seen in that one case, were those noted before immunization?

DR. HEATON: Most of -- it varies with the case, but typically what happened is they have the seizure. Then they got the work-up, and that's when the structural abnormality was detected.

CHAIRMAN OVERTURF: Dr. Farley, did you have one additional question?

DR. FARLEY: I'm wondering if there is anything -- I think it's very useful to do a detailed

look at the febrile or the seizures. Similarly, and probably more importantly, the intussecption, and is there anything to be learned by a very detailed look at both the placebo related, as well as the vaccine related cases to try to look for ways to develop contraindications?

Was there any way of predicting do they share any characteristics that they came in with that might have predicted their developing intussecption?

I mean, we talked about age and those sorts of things, but are there any other -- can we learn anything from that cohort who developed it to say those kids all or some of them shared similarities that we could have excluded them from being eligible for giving this vaccine?

DR. HEATON: That's an excellent question. You know, the study really wasn't designed to look at risk factors for intussecption, and when you look at the characteristics of the children coming into the study who had intussecption versus those that didn't, if you look in the vaccine and placebo groups, there really aren't any differences. I mean, these were

healthy children, and there weren't any differences.

As far as looking into the symptoms, you know, the symptoms are early onset of intussecption, are very general. I mean, the first symptoms are very similar to gastrointestinal illness with typically vomiting. Some had fever. Some had diarrhea, but just from reading through the narratives and looking at them very carefully, I haven't -- my clinical opinion is that there's really no risk factor or nothing that we can pick out that would predict who was going to have intussecption and who wasn't, and that is something certainly that we could continue to evaluate.

CHAIRMAN OVERTURF: We need to go ahead with the second half of the FDA presentation.

Thank you.

DR. IZURIETA: Good morning. I'm going to present some historical data to certain intussecption for use of Rotashield, a brief summary. Most of you are familiar with the data.

The clinical trials, the findings of prelicensure clinical trials were that in those

multiple trials, a total of five intussecption cases, IT, were found in over 10,000 vaccinees for .05 percent versus one case in over 4,000 controls, .02 percent. This difference was not statistically significant. All five cases occurred after second or third dose. Three of those cases did not happen with the final formulation.

When the product was licensed, the package insert described intussecption as a potential adverse reaction. In August 1998, RotaShield was licensed. FDA and CDC monitored passive reporting to the vaccine adverse events reporting system. The Phase 4 was initiated, and in March 1999, the ACIP recommended RotaShield for routine use among healthy children.

In July 1999, the ACIP recommendation for routine vaccine use was suspended based on the following 15 intussecption cases were identified in the vaccine adverse events reporting system, 11 of them during the first week.

Assuming that the expected number of intussecption cases for the first week to have been around 14 and 16, and assuming that the vaccine

adverse events reporting system has a certain degree of under reporting -- in fact, a study published later by Verser (phonetic) from CDC and others found that only 42 or something percent of the cases were reported to VAERS.

Then this considered the signal. Also there were population basis studies which found high, but nonsignificant rates if intussecption within one week following vaccination. This was preliminary data. These range between 292 and 314 cases per 100,000 person-years, assuming a window of risk of one week after vaccination.

MMWR publication did assimilate the reporting to the vaccine adverse even reporting system, and more reports came to VAERS afterwards.

On October 15, 1999, Wyeth voluntarily withdraws RotaShield. This decision was based on preliminary results from CDC's studies.

In October 1999, the ACIP withdraws the recommendation for use, and the license is revoked three years later.

The main study results are that the case

control study and the case serious analysis which were published in the New England Journal of Medicine in 2001 found significant results. In fact, the case control study found the adjusted odds of intussecption for days three to 14 after vaccination to be something like 22 and for three to seven days after vaccination was even higher.

The case serious analysis found a relative risk which was even higher, around 29 for days three to 14 and around 59 for days three to seven. And also the observation that CDC organized study using the vaccine safety data link also found significant results. This study was published by Kramerton (phonetic), his collaborators also in 2001, and the relative risk found was something around 30.

The effect of age at vaccination has been debated since, meaning does age contribute to their relationship between intussecption and RotaShield vaccination. Simonsen and her collaborators showed in her study published recently in 2005 that there could be a certain age interaction, that the later the child was vaccinated, the higher the risk.

In unpublished data so far, Paul Gargiullo from CDC reanalyzed the data from the case control study using conditional and logistic regression and did not find any significant age interaction.

The population at (unintelligible) risk for intussecption, although all the studies may defer the methodologies' strengths, limitations, there was in September 2001 consensus meeting that estimated the attributable risk to one intussecption case per 10,000 vaccinees. This estimate is based on a variate range of estimates from one per 5,000, 4,000-and something, to one per 12,000, and there are even more diverse estimates.

There is like of peer evidence that natural rotavirus infection does cause intussecption. Nonetheless, rotavirus infection may be associated with increased distal ileum wall thickness and lymphadenopathy.

Regarding possible mechanism, RotaShield does contain (unintelligible) strain, and there is a unique strain hypothesis, which was presented by Paul Offer (phonetic), and he could develop that if he were

asked to.

In summary, the evidence indicates existence of a close association between RotaShield and intussecption. This association was identified post licensure. The precise mechanism is still being debated. The consensus estimate of population at (unintelligible) risk could be something around one per 10,000.

And I would like to acknowledge our collaborators from FDA: Myers Braun, Robert Ball, Mary Foulkes, and Douglas Pratt, who are all here, and Paul Gargiullo and Trudy Murphy from CDC, for these comments on this summary.

I'd like very, very briefly to outline our pharmacovigilance plan for RotaTeq if and when it is licensed. Our justification, both FDA and CDC, are committed to insure safety of all vaccines. RotaTeq is a live vaccine.

There is evidence of an association between a prior rotavirus vaccine, in this case RotaShield, and intussecption that could or could not be a class effect here. The association was confirmed

not during the clinical trials, but after licensure.

The main resources that we have for pharmacovigilance are government resources, the vaccine adverse events reporting system, and the vaccine safety data link, which is sponsored by CDC. The sponsor's role would be their own pharmacovigilance plan, which includes auxiliary reporting of adverse events to FDA, which could be sent in monthly batches; the Phase IV, which was discussed earlier; and other resources.

The vaccine adverse events reporting system, as many of you know, is co-managed by CDC and the FDA. It's voluntary, easy to report, nationwide rich. It's useful basically for signal detection.

As everybody also probably knows, VAERS has significant limitations. VAERS will receive auxiliary reporting from the manufacturers which will increase this period which we will find or not useful resource. There will be a daily review of all serious reports and of confirmed and suspected intussecption and of a number of (unintelligible) symptoms.

The limitations include the absence of

denominator data in VSD, the under reporting which could be variable, the missing and wrong data in some of the reports, and usually with some exceptions including anaphylaxisin the first few minutes after vaccination, et cetera. Causality cannot be established using VAERS data.

We also have the vaccine safety data link, which is a collaboration between CDC, the Centers for Disease Control, and a number of health maintenance organizations, and as needed, this agreement gets some feedback from FDA.

There are approximately at this point eight million members, which represent four percent of the U.S. population. The birth cohort is about 96,000 children. It is large. The population is well defined. The databases are linked by computer. It has been done a number of times. It has a great experience.

The initial plan under development contemplates working with automated data at first, but if and when necessary chart reviews could be made. The study could determine the strength of an

association.

Potential limitations in this particular case, the full update of a new vaccine by the HMOs could take a few years. For example, in the RotaShield case initially the update was around 17 percent and varied from state to state and, of course, from HMO to HMO.

Alternatively, in such a case, participation of additional HMOs may be needed or required.

There is also the sponsor's Phase 4 study which was discussed a little earlier. The clinical trials were large, around 36,000 vaccinees approximately, 33,000 or something like that that were followed for one year.

The population studied during the clinical trials, of course, does not necessarily represent those who use the vaccine after licensure. Children with chronic gastrointestinal disease were exclude. Children with some immunosuppressive conditions general, immunosuppressive conditions, were excluded. We don't know about data on -- we did not have

sufficient data on children who were extremely premature, which could be users of the vaccine if it is licensed to everybody.

The proposed Phase 4 study has a sample size of originally I think it was 25,000. It was described today as 28,000. Still, this study is assuming a background rate of intussecption of one per 2,000.

If the study, for instance, were to be done using VSD, there is a study by Kramers which found a background rate of intussecption which was clearly lower than that in children under 12 months of age. It was one in 4,000, which is basically half the rate.

If that were the case, the sample size would have to be multiplied. The same thing if we are looking for a relative risk of two as opposed to relative risk of four. We would need a larger sample size.

The other question regarding the Phase 4 study is the location. Is the location going to be a VSD site, and if so, will there be overlap with

government sponsors? That is, will this be useful or a duplication of effort, assuming that the site chosen is a VSD site, which we don't yet know?

In any case, we think it would be useful to have CDC, FDA and a sponsor conference to discuss details of the way in which the VSD study and the sponsor Phase 4 study could be implemented in a way that we could find a useful resource for each of the studies independently.

That's it. I'd like to recognize Mike Brown, Robert Ball from FDA, Douglas Pratt, as well and Rose Tiernan from FDA, Frank Destefano from CDC, and Trina Haber from CDC for their comments in this presentation.

Thank you.

CHAIRMAN OVERTURF: Thank you, Dr. Izurieta.

We need to adjourn the meeting now and reconvene at 1:15. There'll be additional time for the committee members to address questions to the FDA prior to the questions this afternoon.

Thank you. So we'll reconvene at 1:15.

(Whereupon, at 12:16 p.m., the meeting was adjourned for lunch, to reconvene at 1:15 p.m., the same day.)

AFTERNOON SESSION

(1:21 p.m.)

CHAIRMAN OVERTURF: I'd like to ask the members of the committee, the audience, sponsors to please take their seats. I'd like to call the meeting to order for the afternoon.

The first matter on the agenda is the open public hearing for this period of time, and I'll first ask Christine Walsh if we have individuals who'd like to speak.

MS. WALSH: Good afternoon. As part of the FDA Advisory Committee meeting procedure, we are required to hold an open public hearing for those members of the public who are not on the agenda and would like to make a statement concerning matters pending before the committee.

Dr. Overturf, would you please read the open public hearing statement?

CHAIRMAN OVERTURF: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To insure such transparency at the open public hearing

session of the advisory meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its products, and if known, its director competitors.

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

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

MS. WALSH: We have received one request at this time. Dr. Paul Mendelman would like to make a statement.

Dr. Mendelman.

DR. MENDELMAN: Good afternoon. My name is Paul Mendelman. I'm a Board certified specialist in pediatric infectious disease, and I live in Stanford California. I represent myself.

Specifically, I do not represent Merck or Medimmune, my former employers. To answer the conflict of interest statement, I do have options from Medimmune, but I no longer have a financial arrangement. I'm a non-paid consultant to Medimmune for my institutional memory for particular vaccines.

Today I have two slides, and I will speak for less than seven minutes.

This is the first of two great days for two new live attenuated vaccines that will protect against disease due to rotavirus and Herpes Zoster. The successes of measles, mumps, rubella vaccine over many decades and a varicella vaccine over the past decade are truly phenomenal.

The devastating effects of measles and congenital rubella have been eliminated in the United States, and the control of varicella is in hand.

Congratulations to Merck Vaccine Division.

I worked for either years on the clinical testing of a different live attenuated vaccine, the internasal influenza vaccine FluMist, which was licensed for use in individuals ages 5 to 49 in 2003. The main reason I am here today is to strongly urge this committee and the FDA to reassess the data on FluMist and approve the use of this vaccine in healthy adults 50 to 64 years of age. These adults deserve the option to receive the live attenuated vaccine annually and in the event of a pandemic they deserve the best protection possible.

I want to address why in my opinion FluMist was not approved for this age group previously. FluMist was the first live attenuated vaccine to be filed with the FDA after the problems with RotaShield came to light. In the period just following the RotaShield experience, it seemed that anything alive was feared; anything killed was preferred.

Another and perhaps more important reason that FluMist was not approved for 50 to 64 year olds

was that FluMist was compared to an assumed high efficacy and high effectiveness of the killed vaccine in this age group.

However, there were no and are no available data for the killed influenza vaccine in this specific age group in the literature.

Additional data were not presented to this committee that, in fact, I believe would have led to a different conclusion about the relative effectiveness of FluMist versus the killed vaccine in adults. I would like to briefly present these data to you.

Prior to the 1997 influenza season, we worked with FDA staff on a Phase 3 protocol to assess the safety and effectiveness of FluMist in healthy adults 18 to 64. The study endpoints were prospectively designed to be measured in the overall study population. Four thousand five hundred and sixty-one healthy adults ages 18 to 64 were enrolled and randomized to receive FluMist or placebo mist. The median age of 38 years was chosen for the by age analysis because comparing those over 38 and under 38

to their respective placebo groups provided the largest sample size. These analyses showed that in both age groups FluMist significantly reduced illness.

These data were submitted in the original FluMist application in October of 2000.

There were two relevant VRBPAC meetings for FluMist, one in July of 2001 and the other in December of 2002. At the first meeting, the committee recommended approval of FluMist for use in health adults ages 18 to 64. However, at the second meeting, the FDA requested separate votes for subjects 18 to 49 and for subjects ages 50 to 64.

In fact, only 14 percent, or 641, of the 4,561 adults in the study were 50 to 64 years of age. The reductions in illness were higher in this older subgroup compared to the younger. However, the subgroup was too small to achieve statistical significance.

The committee voted in favor of the safety data, but not in favor of the effectiveness data for those 50 to 64. Although there are no published data on the kill vaccine that examine efficacy or

effectiveness in the subgroup of adults 50 to 64 years of age, for comparison to FluMist there is relevant information that was not presented to the VRBPAC in December of 2002.

In the same 1997 season that FluMist was shown to be safe and effective in more than 4,000 healthy adults ages 18 to 64, the Centers for Disease Control conducted a similar effectiveness study in more than 1,000 adults ages 18 to 64 and found that the kill vaccine was not effective, which is shown on this slide.

And in fact, there was more on this than those vaccinated with the killed vaccine than in those given placebo injections as shown here. In contrast, FluMist was effective for a common endpoint of CDC influenza-like illness.

These results were not presented at the VRBPAC meeting in 2002 because pointing out the inadequacies of the killed vaccine did not seem appropriate pre-licensure strategy.

Another perspective that was considered was the known scenesence of the immune system. Many

vaccines work less well in older than younger individuals, including the killed influenza vaccine. The precedent in decisions of this committee is to recognize this fact.

At VRBPAC meetings for both the acellular pertussis vaccine for adolescents and adults and for the meningococcal vaccine for adolescents and adults, immunogenicity was used as a surrogate for efficacy. Some of the primary endpoints of immunogenicity failed in adults. However, by age subgroup data and separate votes by age were not requested. These vaccines receive the committee's recommendation for FDA approval from adolescents up to 55 and 64 years of age because these were the upper limits of ages tested.

Times have changed since the second FluMist VRBPAC in December 2002. The vulnerability of the U.S. domestic influenza vaccine supply is clear. In the 2003 season, influenza hit early and hard, and there were vaccine shortages.

In the 2004 season, the United States lost one half of its anticipated influenza vaccine supply due to manufacturing contamination of the killed

vaccine.

In the 2005 season, cases of bird flu appeared in the News Daily, and the significant challenge of a global bird flu pandemic remains a growing possibility that we are not prepared to deal with.

This is not the time to be complacent. It is noteworthy that the proof of principle for successful live attenuated H5N1 vaccine has been demonstrated.

Slide 2, please.

After the first major H5N1 human outbreak occurred in 1997 in Hong Kong in which six of 18 people died, a life attenuated H5N1 vaccine was made using the FluMist backbone and successfully protected chickens from a lethal challenge. These data were published in the Journal of Infectious Diseases in 1999.

Thus, I believe the indication for FluMist should be extended to healthy adults 18 to 49 to healthy adults ages 18 to 64. We know more now than we knew three years ago when FluMist was initially

licensed. We know FluMist continues to be safe, and we know that all healthy adults should continue to be protected from influenza through vaccination. We know we do not have enough influenza vaccine, and we know that the live attenuated influenza vaccine, FluMist, has the potential to continue to out perform the killed vaccine.

As a physician, I strongly urge this committee and the FDA to reassess the original prospective FluMist data for the good of public health in the United States of America.

Thank you for your attention.

CHAIRMAN OVERTURF: Thank you, Dr. Mendelman.

Any questions or comments from the committee?

(No response.)

CHAIRMAN OVERTURF: Are there other members of the audience who want to address the committee?

(No response.)

CHAIRMAN OVERTURF: Thank you.

So we'll continue on with the agenda as presented to you earlier this morning.

At this time we're going to have the FDA presentation of questions, but prior to that time, there were a couple of points of clarification that the sponsors of the RotaTeq wanted to make.

DR. HEATON: A couple of things that I wanted to address. The first one is the topic of hematochezia. I covered that somewhat in a bit of a broad overview this morning in the general presentation, but I wanted to go into that in just a little bit more detail for you.

So in the study we instructed investigators that if there were episodes of hematochezia that they should report those and consider those as potential cases of intussecption, that those should be reported to us and that we would submit those cases for potential adjudication.

So we looked at hematochezia in a very comprehensive way. So what I'm going to do is share with you the data. I'm going to start with the overall data in the large scale safety cohort looking

at serious adverse events of hematochezia that were reported among the entire population.

So if I can have Slide 183, please.

So all together as far as serious adverse events of hematochezia, there were 11 cases reported, and when I say "hematochezia," that's any cases of bloody stools, blood in stools. All of those terms were mapped to hematochezia, and that also includes melena or if there was an investigation for hematochezia.

So we had 11 serious adverse events reported out of the 71,799 children. Four were in the vaccine group and seven were in the placebo group, and when we looked at the proportion of cases of hematochezia after each dose, the proportions were pretty similar. We had three in the vaccine group and four in the placebo group after dose one.

There was a one-one ratio after dose two, and a zero vaccine-to-placebo ratio after dose three.

So then the next thing we wanted to do, we wanted to really look at that time frame within 14 days after a dose. The reason why we wanted to look

in that time frame, just to remind you, because of the biology of the virus. We know that the incubation period of the vaccine is about two to three days; that the peak of viral replication is in that four to six-day period after a dose; and that we have replication. It's very limited, for a week after the dose.

So by looking at that two-week period after a dose, we can look at the time period of peak biological activity of the vaccine.

So we looked at that, and actually we saw eight cases within the 14 day period after a dose, two in the vaccine group, six in the placebo group. After dose one, it was one vaccine, four placebo. After dose two it was one vaccine, one placebo, and after dose three, it was zero vaccine, one placebo.

So what we did also, we looked at the cases of hematochezia by the interval after the dose, and we plotted them, and I have that on the next slide.

So this is a summary of the serious adverse events reports of hematochezia by treatment group and by day after dose. We have the number of

cases here on the Y axis. We have the interval after any dose in days on the X axis. The yellow bars represent vaccine recipients, and the white bars represent placebo recipients.

And as you can see, the serious adverse events of hematochezia occurred sporadically and there was no clustering of any vaccine cases at any time during either the 14 day period after the dose or during the entire 42 day period after the dose.

So after looking at hematochezia in the overall population, then we also wanted to focus in on the cases of hematochezia among negatively adjudicated cases of intussecption.

Now, just a reminder. As I said when I started the presentation, that you know, we did encourage investigators if there was hematochezia, that's a symptom of intussecption. So those cases should be reported into us.

And so I have a slide to show you those data. Going to Slide 191, please.

So these are the reports of hematochezia in the negatively adjudicated intussecption cases in

the Phase 3 studies. All together we had 15 reports of hematochezia among those subjects with negatively or unconfirmed intussecption. There were 11 cases in the vaccine group, and this is out of a total of 46 cases that were negatively adjudicated, and four in the placebo group out of a total of 53.

So we wanted to look after each dose and see where these cases of hematochezia in these negatively adjudicated cohort were occurring, and what we saw was that the majority of the ones in the vaccine group were occurring after dose one. We had six in the vaccine group and one in the placebo group after dose one. There was two in the vaccine group and one in the placebo group after dose two, and there were three in the vaccine group and two in the placebo group after dose three.

So then again I wanted to look and see, okay, what about the time period of day, one to 14, after a dose when we know the vaccine is replicating, especially after the first dose.

Well, surprisingly we saw very little during that time frame. The ratio of hematochezia was

two vaccine, one placebo, and then during that time frame after dose two, it was zero-one, and at the same time frame after dose three it was one-zero.

So we looked to see where the imbalance was occurring, and actually it was in the overall 21 day period after the dose. So going on to the next slide, so this is where the imbalance was.

Looking after dose one as I just showed you on the previous slide, there were seven total reports, six in the vaccine group, one in the placebo group. So what we did is we looked very carefully at each of those cases of hematochezia, and this is what we found. Pardon the detail, but I think it's important to just step through these.

So for the six cases that occurred, we had one on day three. That was a child with vomiting and irritability, and he had had hematochezia the mother reported on some days between days three to 12 post vaccination.

We had a case that occurred on day ten, and the mother reported blood in the stool on defecation, and there were three episodes. There was

one on day seven, one on day 12, and one on day 13.

The third case that occurred was in a child who was constipated and after a soap enema, the mother reported that the child had a bowel movement with a jelly-like bloody stool.

We had one on day 16 where a child had bright red blood per rectum and was referred to a surgeon; had no other symptoms. The exam was totally normal. They were treated with amoxicillin, gentamicin, and metranidazole.

Another one on day 16. There was an episode of one explosive stool with currant jelly, mucous and blood. It was brought out positive. However, the exam was normal. There were no further episodes, and no further work-up was done.

And then finally, we had a child on day 21 who had blood on the feces with diarrhea. The physician suspected a milk allergy, although the IgE for milk protein was negative, and actually switched the formula and the child did well and there were no other episodes of blood on the feces with that child that were reported.

Now, in addition to these six vaccine cases, we had a single placebo case on day seven of a child that was irritable, with blood in the stool that was guaiac positive.

So the overall incidence, again, of hematochezia is small in the overall population. We saw this imbalance in the absolute numbers of cases of hematochezia after dose one, but again, the time frame was not during the time frame when the virus is at its peak of replication, and I think as you can see here, the investigators were doing what they were supposed to do and reporting all of the cases of hematochezia to us, but certainly there are several of these that represent uncomplicated cases.

CHAIRMAN OVERTURF: Any questions? Yes, Dr. Farley.

DR. FARLEY: It seems like the numbers are a little different between Dr. Tiernan's presentation, numbers of hematochezia in the negatively adjudicated, and maybe in the positive as well. Well, maybe that's irrelevant, but in the negative in particular. I think she has at least 26 that she was reporting on.

Why are the numbers different?

There were some other areas where there were some number discrepancies.

DR. HEATON: Yes, I have to go over those. The way we did this is we read the reports, the narrative reports and the four reports of hematochezia. So what I've shown you, the first set of data I showed you with the 11 cases were serious adverse event reports of hematochezia in the overall population.

The second set of numbers was the hematochezia within the negatively adjudicated cases of intussecption, and I believe Dr. Tiernan's numbers were ten-three, and I have 11-four, and that's because I combined Protocols 7 and 9 with Protocol 6. So that's why the 11 cases of hematochezia there and a total of 11 and four.

The other difference, I think Dr. Tiernan was also looking at some of the non-serious AEs as well of hematochezia. So that may be another difference also.

DR. TIERNAN: I include currant jelly,

too. I don't know if you included that.

DR. HEATON: Okay.

CHAIRMAN OVERTURF: Any other questions?

(No response.)

DR. HEATON: Okay. Thank you very much.

CHAIRMAN OVERTURF: Thank you.

Dr. Markovitz has one question.

DR. MARKOVITZ: This actually goes back a little ways in your previous presentation. I was curious. When you talk about intent to treat, obviously people who got one or two doses of the vaccine would drop away or are included where they would have dropped away in your whole -- you know, in your more complete analysis.

So who else drops away or is it just people who got or I should say -- I'm not sure if I'm making myself clear.

So when you're talking about intent to treat, who's included in that group?

DR. HEATON: Yes. We include all kids starting from the first day of vaccination. That's what we call our intent to treat population.

DR. MARKOVITZ: Who are you losing though? So later when you analyze people who have had three doses and are subject to your -- sort of the analysis that you're primarily presenting to us, who are you losing from the original intent to treat in that?

DR. HEATON: Sure. Yeah, the primary reason for a subject not qualifying for the protocol analysis is not receiving all three doses of vaccine. That's by far and away the primary reason. Other reasons include if they had an episode of rotavirus before they got all three doses, then clearly we can't count those kids in the per protocol post dose three analysis. So that's another reason.

If they had missing data, for example, the parents will submit the stool sample and would forget to submit the diary card or vice versa. So that's another reason as well.

So those are some of the primary reasons why children would be excluded from the per protocol analysis.

Does that answer your question?

DR. MARKOVITZ: Yes.

CHAIRMAN OVERTURF: Dr. Farley.

DR. FARLEY: A question about the children who had intussecption that went to surgery. Are there pathology results on them?

And you mentioned one that had the benign report hyperplasia. Is that a common finding and is that typical in all cases of intussecption?

DR. HEATON: So the question is about pathology findings with cases of intussecption, the child with the benign lymphoid hyperplasia. The child in Protocol 5 went to surgery, had benign lymphoid hyperplasia, and that is a common finding.

The etiology of intussecption is somewhat unknown, but it has been associated with respiratory adenovirus, and there have been case reports with other bacterial E. coli of 0157, campylobacter, yursinia. Oftentimes these kids have mesenteric adenitis. So that has been thought perhaps it's the lymph adenopathy might be one of the explanations for the pathogenesis of intussecption.

As far as children in our studies, you know, most of them are reduced with an enema. Some

did have surgery, and many of them though just had surgical reduction and didn't have resection, and if they did have resection, it was usually just a small amount.

In fact, you know, the outcomes of the children with intussecption were good. Unfortunately, we had the one death that we reported, too, that occurred 98 days after dose three in the child who got sepsis after surgery, but other than that, children recovered. We didn't have children with ileostomies and colostomies. We did not have children who had short gut syndrome or any ongoing complications.

CHAIRMAN OVERTURF: Dr. McInnes.

DR. McINNES: I wonder if you have any sense around the incidence or prevalence of intussecption in younger infants compared with children under two, children under one. Do you have anything that breaks that down further? Are there any data on that?

In looking at how old some of these children might have been on receipt of dose three, they're pushing up close to six months, right?

DR. HEATON: That's right.

DR. McINNES: If not a little more.

DR. HEATON: That's right.

DR. McINNES: How many preterm infants did you have in this study? And I understand they were immunized by chronological age, but were there any cases of intussecption in preterm?

DR. HEATON: So the question is about cases of intussecption in preterm infants. Overall we enrolled over 2,000 premature infants. They ranged in gestational age from 25 to 36 weeks, and of course, they were enrolled according to their chronological age. We did not have any cases of intussecption among premature infants.

CHAIRMAN OVERTURF: Dr. Royal.

DR. ROYAL: Yes, I wonder if it might be worth commenting on whether or not in a study where one is looking out for complications such as intussecption that one might be able to avoid the development of that by early intervention and whether or not in that sort of situation you may see a lower incidence than what one would otherwise.

DR. HEATON: So the question is could we be seeing a lower incidence of intussecption because we are doing active surveillance. And you know, we actually thought about both ends of the spectrum.

You know, one concern was since we're actively looking for it, could milder cases come to our attention and we end up with a higher rate of intussecption than what we had anticipated. So that was one end of the spectrum.

On the other end, you know, the question could be because there's intervention in the study setting, could those cases, you know, be somehow treated -- I always think of the example of gastroenteritis, and if there's intervention in the study setting and you're providing oral hydration solution, you might decrease the severity of it.

But I think it's different with intussecption because there's such a clear diagnosis. I mean, the bowel telescopes in on itself. It gets caught. Spontaneous reduction is uncommon. There are reports, but they tend to be more in older children. So if the bowel is caught and the vascular supply is

compromised, if the child doesn't come to medical attention, their outcome is grave.

So I think that it would be likely even with the study intervention that we would be picking up the cases, and I think that's also exemplified by the background rates that we found because overall and in the placebo group the rates were right at one in 2,200, which is what we had assumed based on published reports of background intussecption.

CHAIRMAN OVERTURF: Dr. wharton had a comment.

DR. WHARTON: Based on the experience you've presented here, my assumption will be that the proposed indication will be for use in the vaccine series beginning at six to ten or six to 12 weeks of age. I wish all children began childhood immunizations on time, but many of them don't, and my expectation would be that in spite of what product labeling may say, some children will initiate the vaccine series late.

How will that be monitored post licensure?

DR. HEATON: That's a very good question.

So the question is about the age at first dose. The fact that there are going to be infants who are older than 12 weeks who are going to get their first dose of vaccine regardless of what the labeling says, and certainly we're going to be monitoring this carefully in the post licensure setting.

We can only recommend what we've studied in our clinical trials, and that's certainly what we'll put forward as the recommendation in the label.

However, I can tell you from some of our Phase 2 data that in the older infants who were enrolled in the Phase 2 studies, the vaccine was well tolerated. We didn't see high fevers. Incidence of fever was similar in vaccine and placebo recipients, and as well as vomiting and diarrhea.

But we will monitor this in the post licensure setting, certainly with passive surveillance when we get the reports of intussecption we are going to be actually making follow-up telephone calls and getting more information about those cases. So should, you know, older children get the dose -- get doses at older age in cases that occur, certainly

we'll be monitoring that and certainly be monitoring it also in the active surveillance as well.

CHAIRMAN OVERTURF: Dr. Markovitz.

DR. MARKOVITZ: Yeah. Of course, our charge here is mainly to deal with issues that will affect the American public, but, Dr. Heaton, you seem to have been involved in this project for quite a long time, and it's obviously extremely important to know what Merck's plans are for the rest of the world where most of these 500,000 people are dying a year.

Does Merck have a plan to distribute this to poorer countries in any fashion?

DR. HEATON: Yes. So the question is the plan to distribute the vaccine to poorer countries, and I'm very happy to announce that last week we publicly announced that we are working with the rotavirus vaccine program and with the Gates Foundation to be starting to do studies in the developing world.

Certainly, given the history of the previous rotavirus vaccines and their efficacy in the developing world we do need to evaluate the vaccine.

It is an oral vaccine, and you know, children in the developing world, malnourishment or if they're a colonizer of other enteric pathogens, may not have the same immune response to the vaccine as healthy children.

So we do want to evaluate the efficacy of the vaccine in those populations, and we plan to start trials in Asian and Africa by the end of next year.

CHAIRMAN OVERTURF: Will that include children who are getting oral polio vaccine?

DR. HEATON: That's right. In fact, we have an ongoing study now to evaluate concomitant use of RotaTeq and oral polio. It's going on in Mexico, Costa Rico, Guatemala and Brazil.

CHAIRMAN OVERTURF: Dr. Malonardo.

DR. MALONARDO: A quick question. Did you analyze the role of breast feeding? Is there any difference in terms of efficacy of patients getting breast feeding? Did you look at that?

DR. HEATON: Yes, we actually collected breast feeding data on all 70,000 patients and quantified that, and then we looked at the efficacy of

the vaccine according to breast feeding in the efficacy cohort, in that subset of about 7,000 kids.

And so what we did, we categorized infants according to whether they were ever breast fed or never breast fed and infants who had a mixture, and we actually collected the breast feeding data at each vaccination visit. So it was their breast feeding status at the time they were receiving vaccine.

And so I have that slide here for you. Slide 164, please.

So this is looking at the efficacy of our RotaTeq among infants who were never breast fed, had some breast feeding, and were exclusively breast fed, and what you can see is the efficacy in this group is quite similar to what the overall efficacy was.

The efficacy in the group that was never breast fed against any severity of disease was 68 percent, and recall the number I showed you this morning was 74 percent. Efficacy for children who had a mixture of some breast feeding and some formula feeding was 82 percent, and efficacy in children who were exclusively breast fed was 68 percent.

CHAIRMAN OVERTURF: Thank you, Dr. Heaton.

At this time I'd ask the FDA to come forward. They're going to present the questions for the committee.

DR. TIERNAN: So the first question: 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, example, G9, when the first dose of vaccine is administered at six to 12 weeks of age, followed by two subsequent doses, separated by four to ten week intervals?

And if not, what additional information should be provided?

We'll do the next one. Are the available data adequate to support the safety of RotaTeq when used in a three-dose series beginning with the first dose at six to 12 weeks of age, followed by two additional doses, separated by four to ten week intervals, and if not, what additional information should be provided?

And then the last question: please

identify any other issues that should be addressed, including post licensure studies. In particular, please address the assessment of intussecption, the applicant's proposed pharmacovigilance plan, concomitant use with other routinely administered vaccines, and the use of the vaccine in immunocompromised children, such as those with HIV or children taking steroids or other chronic immunosuppressive therapies or other special populations.

CHAIRMAN OVERTURF: I think we will actually do these in reverse order, but first, before we do that, I had left some time here to address any other questions that were brought up in the FDA presentation. So if anybody has any questions, this would be the time to ask them.

DR. SELF: Yeah, there was a question about the post licensure plans for documenting your ability of protection years three through five. I wonder if we could return to that.

CHAIRMAN OVERTURF: the question is does the sponsor or the FDA have plans in regard to looking

at the durability of protection in post licensure.

DR. TIERNAN: So the question about looking at efficacy or durability of efficacy post licensure, I think it's really important. The first review of this disease and where it's the most problematic, the bulk of hospitalizations and emergency department visits for rotavirus do occur in kids age two and under. About 75 percent to, depending on what country you're talking about, about 90 percent occur in younger children.

So, you know, our really target group is making sure that we're preventing the severe disease and preventing those hospitalizations and emergency department visits and office visits in those younger infants.

Now, if you recall, the efficacy data that I showed you for the second season against severe disease was quite high. It was 88 percent for the efficacy cohort, and then there was, you know, about 90 to 95 percent protection against hospitalizations in the second year of life.

So based on those data, you know, it

indicates that there will be some protection that will persist through the third and fourth years of life, and by the time the child gets to the third and fourth year of life, they're a lot less vulnerable to the severe complications of dehydration from rotavirus gastroenteritis.

Having said that, we're certainly doing effectiveness studies in the post marketing period in Latin America. We'll be looking at these kinds of issues and considering it though we don't have final plans now.

CHAIRMAN OVERTURF: So I think I will open up the floor to the committee to consider actually the third question first, which is the Questions 3(a) through 3(d), which include the assessment of intussecption, the applicant's proposed pharmacovigilance plan, the common use with other routinely administered childhood vaccines, and the use of vaccines in immunocompromised children, such as those with HIV or children taking steroids or other chronic immunosuppressive therapies, other special populations.

There will be no vote on this particular question. So what I would like is comments from the committee in regard to those populations specifically. It would seem very clear to me that the sponsor's presentation clearly raised questions regarding the concomitant use with other routinely administered childhood vaccinations in that I think the issue of its effect upon both serologic, as well as perhaps efficacy or effectiveness of other vaccines really needs to be explored further, particularly in regard to DTAP.

So that seems to be something that needs to be necessarily done during the follow-up and needs to continue to be done.

I think it's also likely as Dr. Word pointed out that in today's world of public health, the ever expanding list of options for vaccines for pediatricians increases. So this may be vaccine specific. So that's going to have to be looked at probably as well, and also the schedules vary tremendously because of missed opportunities and other things in the pediatrician's offices. So that

question is going to have to be addressed as well in follow-up studies.

And I've already addressed that, and it wounds like there are plans to address the issue of oral polio vaccine, which I think is going to be critical for this vaccine, particularly since it's going to be so intensively used probably outside the United States in countries that use oral polio for their immunization program.

And I think it's also clear that the use of vaccine in immunocompromised children, HIV, steroids and other chronic immunosuppressive therapies, the population will have to be addressed, is often addressed with vaccines in the post licensure period and will have to be looked at critically, probably with formalized studies because of the at least potential risk of some of these vaccines in those groups.

So are there other comments regarding these questions? Yes, Dr. Self.

DR. SELF: So my comment has to do with the pharmacovigilance plan. Let's see. Where to

begin.

The data that's presented in our favorite Slide 51 has an upper bound for the relative risk within the 42 day window of intussecption of five, and in the presentation of the observational study that you're planning, if I read, I think, the last in a series of slides that was presented about the design of that study, there would be fairly good power to detect an increase in risk or about fourfold. So there's a fairly small increment that that study will provide in refining the relative risk of intussecption.

It's an uncontrolled study, and so there are some other uncertainties involved there as well. So I guess in summary, it wasn't clear to me that the observational study as planned, although impressive in size, would actually deliver an important additional degree of security about the safety of the vaccine with respect to risk for intussecption.

So there are some consequences and issues to address. One is in considering for the U.S. what the right balance is of risks and benefits, just, you

know, what kind of bound on the relative risk of intussecption needs to be established to make this sort of a viable regimen for the U.S. So I'd like to hear a comment on that.

Second, the trial is designed. You surely have thought about other designs and, you know, maybe larger trials. If you could share some thoughts about arriving at the 28,000 sample size for that design and what the potential is for having a larger study.

Three, where were you going to take the baseline estimates of risk from to use in order to get some assessment of relative risk?

Maybe I'll stop there.

CHAIRMAN OVERTURF: While you're taking that, I also would like clarification from the FDA on this point. Dr. Izurieta made some comments regarding the use of VAERS, VSD, and the study which would answer in part some of your questions in that there would be larger groups if they did not overlap. In other words, if the data provided by the sponsor were separate and apart from the VSD and the BURGHS groups, the population bases would be different.

So I guess I would favor an approach that would look at all of these bares and not have overlapping populations, which would help increase somewhat, although there would be different -- it would be slightly different, but it would still, I think, provide a larger population base.

DR. SELF: Yeah. There are good things and not so good things about the VAERS system, and estimating relative risk from the VAERS is probably not one of the strengths. So I think that part will rely much more heavily on this proposed observational study.

CHAIRMAN OVERTURF: I think VSD though would provide some of those same standardizations that you might see with a prospective study done by the sponsors.

So would the sponsors like to address that question anymore?

DR. HEATON: I will start and then I will have Chris or Joe come up to and to fill you in on the technical details.

We're really looking at this

pharmacovigilance plan as it has many pieces, and all of the pieces, you know, will need to come together to give us the overall picture of the safety of the vaccine in the real world setting, and that's what we want to do: establish the safety of the vaccine in the real world setting.

So one thing I want to or a couple of things I want to point out, as far as the background rates, we can start with the easy questions first. The background rates, we are actually going to be assessing the background rates in the population that we're going to be studying before the vaccine is actually launched there.

So we should have, you know, as accurate background rates as possible before we actually start the study, well, before we actually start using vaccine there.

And, again, the background rate of one in 2,000, you know, that background rate has been questioned in the past, but it certainly is what we saw in the placebo group in our Phase 3 studies.

Secondly is that I think it's important to

remember the purpose of this post licensure surveillance is not to ultimately define forever and ever what the relative risk of intussecption with RotaTeq is. The purpose of it is we want to detect a signal. If it exists, we want to detect it quickly, and we want to know that, and we want to be working with CDC, FDA to investigate that.

So that's why the stocking boundary has been or the signal boundary, I should say, the signal boundary that Chris showed you earlier today has been set up so that if we have relative risk levels of four, of ten, that we will pick that up, as he showed you earlier today, very quickly with a low number of subjects.

And then as far as addressing what overall upper bounds that we can show at the end of the study, that's really going to depend on how many cases that we see, and I think that I would like to now turn it over to Chris and Joe to get into some of those numbers with you because I think what you're going to see is depending on the number of cases that we're going to be able to refine that upper bounds quite a

bit.

If we don't have an increased risk of intussecption, we're going to be able to refine that upper bound from a level of five downward, and I'll let Joe talk to you about that.

DR. HEYSE: Yes, I just want to try to quantify some of Dr. Self's perceptions as to what the study will and will not be able to demonstrate. So what I really want to do is just go over some of the typical operating characteristics of the post marketing surveillance plan.

Dr. Mast outlined the basic concept of the trial, which Dr. Heaton just reviewed where the main feature is really to generate signals, and the idea is to generate signals earlier if the relative risk is actually higher.

Now, we did use, just for purposes of setting, a provisional sample size. We did use a relative risk of four, and the chance of hitting the boundary that Dr. Mast showed you, assuming a background relatively risk of one in 2,000, is about 96 percent, which we felt was a very strong number.

Obviously, for lower relative risk the probability of hitting that signal line is less, and for the numbers between two and three, it's actually between 40 and 80 percent, 80 percent for a relative risk of three and 40 percent for a relative risk of two.

So for those lower relative risk, in that range, the idea would be that we would have to complement this with the other data that does exist on intussecption, like the data from REST with what we know about that, and then other post marketing activities through CDC and elsewhere.

To give you one idea, again, I just want to quantify what we would get at the end of the study. What you may not have been able to determine from the graph that Dr. Mast showed you is that in order to get through this period and not hit a signal would require eight or fewer intussecption cases observed among the 28,000. This, again, assuming a background rate of one in 2,000 would be adjusted accordingly, is a relative risk of 2.3 with an upper bound of 3.2.

Obviously if fewer cases than eight are

observed, then the observed relative risk would be lower than that, as would the upper bound of the confidence interval.

So, for example, if we observe six cases, the observed relative risk is 1.7 and the upper bound of the confidence limit is 2.6. So the idea here is to give you some numbers as to, you know, what would be considered satisfactory or unsatisfactory. Okay?

Does that answer your question?

DR. SELF: One of them. So I guess I'd also like to hear something about your thoughts of risks and balances for the U.S.

DR. HEATON: This is a question of what level of risk do we need to be able to rule out, if you will, for the U.S., and this is a question that we asked six and a half years ago when we stood right here in front of this group, and it's a question that we have challenged people with, and I think what's great today is we can come to you with data.

And what we have seen in the REST trial is that there's no signal that there is an intussecption concern with this vaccine. The overall number of

cases within the 42 day period after a dose was six in the vaccine group and five in the placebo group, and when you look in the 365 day period after a dose, there were 13 in the vaccine group and 15 in the placebo group.

There were no cases of intussecption within the two weeks after dose one, and there was no clustering of cases of intussecption after any time.

The overall AE profile looks good. There's no excess fever. There's a 1.3 percent increase in vomiting and diarrhea after dose one. The hematochezia in the overall population was actually higher in the placebo group than the vaccine group.

So one can never prove the absence of risk, but the safety data strongly support from REST and the other two phase three studies, strongly support the safety of RotaTeq.

The other thing that we do know is that this vaccine reduced hospitalizations by 96 percent. There are 50 to 70,000 hospitalizations that occur every year in the United States. By the time a child reaches their fifth birthday, they have a one in 65

chance of being hospitalized with rotavirus. One out of 17 babies end up in the emergency department. One out of ten end up in the pediatric clinic.

So we know those data. If the vaccine works in the clinic like it has in the clinical trials, and we have every reason to believe that it will, the potential benefits are dramatic, and we don't see any signal of any safety concern.

So based on the data that we have in front of us, I think we can say with high confidence that the benefit of this vaccine greatly outweighs any potential risk.

DR. SELF: So the one in 65 is one that I sort of plucked out trying to do my own quick calculation, and then with a background rate of intussecption of one in 2,000, applying relative risk to that, certainly you don't get the two rates close to each other unless you get quite high relative risks.

What I don't have a sense of is how to balance a hospitalization that is sort of generically due to rotavirus to the severity of the

hospitalization that is due to a case of intussecption, and it's that balance that I'm kind of grappling with and I don't have background to get a sense of. Could you comment on that?

DR. HEATON: Certainly. I guess before making those comparisons there's no indication of an increased risk of intussecption. So I think that's really important for us to remember.

But the overall mortality rates from the two diseases are identical. There's about 20 to 60 deaths from intussecption in the U.S. every year, and it's about the same number of deaths from rotavirus gastroenteritis every year.

As far as typical presentation of intussecption, in our study most of the children were diagnosed early. There were treated with a barium enema. So that typically involves either just observation; they are treated with an enemy and then they're observed for a few hours or maybe overnight, and then they go home.

For those with surgery, their hospital stays may be about four to five days, but that is only

about a third of the cases.

For rotavirus gastroenteritis, on the other hand, what we know is for hospitalizations on average it's about two to three days per hospitalization, depending on the study that you're looking at.

So I think what we've got is a very common disease that children are at high risk from, rotavirus, and we've got a vaccine to prevent it, and then on the other hand, we have a theoretical concern about something that's very uncommon and that the medical complications overall are similar.

CHAIRMAN OVERTURF: Dr. Karron.

DR. KARRON: I think a couple of issues related to pharmacovigilance. The first is that in terms of follow-up both perhaps through the plan that the sponsor presented and also through some other mechanism, such as vaccine safety data link, I think it would be important also to look at this issue of seizure that was raised, febrile and afebrile seizures.

The other comment I wanted to make was in

terms, I guess, of Item D, which is the special populations, and I was interested to hear that actually in terms of premature infants, that a fairly large group, 2,000 infants were studied, and that the age range was gestational age, was 25 to 36 weeks. I think it would be useful; perhaps the sponsor has more information now that they can present about the distribution of age. Do you?

Because if -- well, why don't I stop there, and if you have it, it would be interesting to see that.

DR. HEATON: Yes, we did enroll over 2,000 premature infants. Gestational age was 25 to 36 weeks, and I can tell you -- let me just tell you how they fit into the study and give you some background.

So recall that we followed all subjects for serious adverse events, and then we followed a subset of subjects for detailed safety, all serious and non-serious adverse events, and then we also followed a subset of subjects for efficacy.

So I can just verbally share with you that the overall SAE profile among the premature infants

was identical to the overall population, as was the AE profile. Actually there wasn't a statistically significant increase in vomiting and diarrhea, and no statistically significant increase in fever in that group.

Now, in the group that we evaluated for efficacy, we had a little over 200 subjects in that group, and if I can get those data for you, I can tell you while they're pulling that up that the efficacy in those subjects was, again, very similar to what it was in the overall population.

Efficacy, again, severe disease was 100 percent. We only had two cases of severe disease. They were both in the placebo group, and then the overall efficacy against any severity of disease was 70 percent.

So as far as other compromised populations, if you will, one thing that I failed to mention earlier is that as part of our developing world studies we are doing a rather large trial in infants born to HIV positive mothers, and we are going to be looking at the safety of the vaccine in children

who are both HIV infected and HIV uninfected as well.

DR. KARRON: Just one question in follow-up. Do you have any concomitant vaccine immunogenicity data in premature infants or they weren't part of that?

DR. HEATON: No, there weren't enough subjects in that substudy to evaluate that.

CHAIRMAN OVERTURF: I have a special population that pediatricians now see a great deal, are children who have compromised guts. They actually have short guts or malabsorptive syndrome, some of which are congenital.

So I guess my question would be: has anybody looked at this specifically in terms of both safety and immunogenicity, but particularly whether it gives us any clues to what part of the gut is important in terms of the immune response to this virus.

DR. HEATON: Well, the immune response, the virus actually attaches in the upper part of the small intestine, and that's where the replication occurs. It replicates in the mature epithelial cells

there.

CHAIRMAN OVERTURF: Anyway, that should be another population that probably needs to be included in the special population obviously, are those children with compromised guts.

Dr. Royal.

DR. ROYAL: We've seen the data for the reduction in hospitalizations, emergency department visits and office visits for the vaccine versus placebo group. Can you say anything about what one would see if you compare the placebo group to just the general population, whether there's a difference in those rates?

DR. HEATON: Yes. I have a lot of epidemiology background. So it's very tempting for me to want to compare the rates that we saw in the placebo group with background rates and try to do an easy epidemiology study.

But there are, you know, so many factors in a clinical trial setting that can actually affect that that I think we have to be careful about extrapolating epidemiologic data from clinical trial

data.

As they showed in a study in Peru just by the actual intervention of the study personnel, they think that that actually affected the outcome of the trial, and so we have been very hesitant to do that, but overall the attack rates vary by region. In the placebo group they were highest in the Navajo and White Mountain Apache nations, somewhat in the middle in Finland, and lower in other areas in the U.S.. So the overall attack rates varied, but what did not vary was the reduction in the rates of hospitalizations and emergency department visits. That reduction was consistent across all of the regions.

CHAIRMAN OVERTURF: I would like to ask Dr. Izurieta -- I would just like anybody at the FDA who could give me the question. Do you know what the potential cohort would be in the VSD segments of post licensure studies?

There were a number of eight million members that were now enrolled in that, but does anybody have an idea what the potential cohort would be for rotavirus studies?

DR. IZURIETA: Yeah, there is no final number yet. That data is being calculated today by the CDC group as part of the plan, but just to have an idea, if we were to assume that -- let's assume the VSD population at this point, probably the best data for the VSD population on background rate would be what Komars published, which could be one in 4,000. This could be debated or not, but that's what we have that comes from the real VSD population. So I think it's as reasonable as any other estimate, probably better than getting data from outside sources.

Assuming -- and this is quick under epidemiology -- but just to give you an idea, assuming a 90 percent power and assuming that we want to find a relative significant result for a relative risk of two, you know, twice as large as the expected background rate, under all these conditions and assuming no other complications deriving from the specific methodology that's going to be used by CDC, which is a rapid cycle analysis under certain assumptions with that, but oversimplifying -- and this is really oversimplifying -- we could think that we