are studies, additional studies planned on these issues, and I just would like you to kind of crystalize what those studies are, if you wouldn't mind.

And secondly, the issue that was raised earlier about the concern about antigenic drift, if you will, the report from the Netherlands, and to me that is also an area that needs to be better defined with these vaccines.

DR. MESCHIEVITZ: Yeah, let me comment, again, briefly. We are committed to doing a post marketing study, and we're in discussions with FDA currently about the final design of that study. We will included in it -- it's a computerized system where we can gather information on severe types of reactions that we often look for in these trials.

We'll also be designing it to specifically look and characterize the types of local reactions that have been presented today, and obviously the discussion that's occurring around the table today is helpful to us in fine tuning the design of that study to look at the questions that are being raised.

So the study hasn't begun yet, and comments made today can be incorporated into that. So specific ideas that you have would be of value.

DR. STEPHENS: Just to emphasize the need for mechanistic as opposed to descriptive data, I think that we have a lot of descriptive data, but we need more --

DR. MESCHIEVITZ: We hear that loud and clear, yes.

CHAIRMAN GREENBERG: Ms. Fisher.

MS. FISHER: I assume we are all voting today for the administration of the fifth dose in isolation. In other words, the data that we've been shown I would assume did not include the simultaneous administration of MMR or polio or chicken pox vaccine. so we're looking at this in terms of a fifth dose in isolation?

CHAIRMAN GREENBERG: Yes.

MS. FISHER: Okay. But in the real world, you know, most often the children are receiving other vaccines on the same day. Is there any other data regarding the administration of this fifth dose in combination with other vaccines?

DR. FINN: No. This is Theresa Finn.

I think that what can be given or is sometimes given with this particular dose is varicella catch-up and MMR, but we have no data on simultaneous administration of those products, and I'm not sure

that they are always given together with the DTaP at fifth dose.

MS. FISHER: Polio also.

Well, I think that's extremely important. I know that there's a lot of concern in the public about the fact that when these vaccines are licensed, they're seen independently, but in practice they're given in combination simultaneous, and I, for one, would like to see more data, and especially mechanism data showing what happens in the body when you give all of these vaccines on one day.

CHAIRMAN GREENBERG: Dr. Estes.

DR. ESTES: My comments echo most of those. I think it's critical to understand mechanisms of reactogenicity and correlates of protection.

I again will just bring up the one other point that I made earlier. The data we saw today from the German study and apparently even the NIH study was really all safety data in Caucasians, and so I am struck by the fact that we don't have any data in other ethnic groups, and it would seem to me that even before licensure that's an issue that needs to be looked at very carefully.

CHAIRMAN GREENBERG: Dr. Ferrieri. Oh, I'm sorry.

DR. HARTIGAN: Oh, that's okay. I don't have anything --

CHAIRMAN GREENBERG: My peripheral vision is going. Dr. Hartigan.

DR. HARTIGAN: -- anything to add, except that is there any data to indicate that the acellular pertussis, now that we have a big cohort that have been vaccinated only with acellular pertussis vaccines; is there any different incidence of pertussis in this current age compared to historical ages where they had whole cell vaccine?

DR. LIVENGOOD: The data suggest right now that there's been really no change in the pattern of incidence of pertussis among young children. There have been changes over this decade. Primarily I believe it's through increased recognition, the detection of disease in adolescents and young adults. Those are the populations that have greatly increased.

But the best vaccinated population, those one to four, have been just flat during this whole transition period. So I don't think there's any reason to have concerns about efficacy or lack of effectiveness in terms of the acellular products. I think they have performed quite well.

CHAIRMAN GREENBERG: Thank you.

Dr. Ferrieri.

DR. FERRIERI: Nothing beyond what I had suggested earlier, but I'm so pleased to hear about this cohort study that will permit study of issues that we've brought up today, and that we go beyond just reporting very important adverse reactions, but come to a basic understanding.

So it's an opportunity for PMC to really raise the yardstick here, what the expectations are.

DR. PETER: One of the advantages of sitting on this side of the table is that everybody has already made excellent suggestions. In fact, I've noticed when we go from Dr. Kim and move to the right that the persons' comments become less and less.

So I've already said my mandatory 20 seconds, and I have nothing further to add.

(Laughter.)

CHAIRMAN GREENBERG: Dr. Livengood.

DR. LIVENGOOD: I'd just like to make two points, one of which is I am concerned with the acellular products about the differing amounts of tetanus and diphtheria in them for reasons that vary quite a lot. This product is the one with the lowest amount of diphtheria of the acellular products, and there may either need to be some attempt to bring them

into closer harmony across products or one thing we may need to do is if we may need for diphtheria to have different recommendations about number of doses for different products, which of course would be something I would prefer not to have to deal with.

And the other thing would be about the mechanistic thing of biopsying these lesions. We worked primarily with VAERS, and I think the time lag for VAERS is going to be so long that this isn't going to be something that we can study through the traditional post marketing surveillances.

So I hope that the FDA really works with the manufacturer to set up mechanisms by which these things can be detected early at times in which biopsies or other information can be obtained very quickly.

CHAIRMAN GREENBERG: I just want to ask a question here. Precisely what would get biopsied if one was going to do a biopsy? Is biopsy a feasible intervention to address these lesions? I would have assumed that it was a relatively deep biopsy that was not going to be generally acceptable.

Does anybody know? Dr. Ferrieri, you raised the issue of biopsy, which I would love to have the tissue, but is it obtainable?

DR. FERRIERI: Well, thank you for keeping us all very honest, Harry, because it would be very easy if it's a nodular type lesion, but that isn't what is seen. You have a huge surface area that, and if you just do a, you know, random biopsy, you may not learn very much. You'll have nonspecific inflammatory change is my prediction.

So although I'm keen on understanding it, the limitations of my suggestions are the lack of an organized type lesion that might be better able to be probed for various things. One could study any number of molecular markers, immunological pro inflammatory markers, et cetera.

So I see it as a problem. There may be people in the room who think that in the very severe reactions you do have a central, key part of the whole process, but that's not my impression.

Would someone else corroborate that, that it's diffuse, widespread with no central key lesion to go after most of the time?

DR. SNIDER: Kathy is shaking her head yes.

DR. FERRIERI: You agree, Kathy. So this is a real problem.

DR. EDWARDS: I think the other thing is,

too, the biopsy would convert those mild and moderate pains to severe pain.

DR. FERRIERI: Yeah, right.

(Laughter.)

DR. FERRIERI: And my concern is then we'll have Group A streptococci invade the biopsy site, and then we're really going to have problems.

CHAIRMAN GREENBERG: I would just add here that the manufacturer be aware of the fact that there's really incredible progress being made as far as visualization, noninvasive visualization with a variety of functional scanning and X-ray modalities, and if the time is not right now, it will be within the next couple of years where resolution is going to be really extremely fine, and that you may be able to get pictures of what is going on noninvasively in these limbs, and you should keep exploring that with good radiology departments.

The last person is Dr. Myers.

DR. MYERS: And I'd just add that this may be a place for animal models to explore the pathophysiology.

I guess everybody has said everything I'd say, too, except I'd like to really emphasize the racial disparity in the study populations. As the

African American and other minority groups have a disproportionate amount of pertussis, I think it inherent that these vaccines be studied carefully in those populations as well. I think there is a deficiency there.

CHAIRMAN GREENBERG: Well, and for the record, I agree with all my committee members. You've done a great job, and we've finished 50 minutes early today, which is a record.

I would like to thank you.

Does the FDA -- did they get all of the information that you want to get from this?

Okay. Thank you. We'll see you all tomorrow.

(Whereupon, at 5:10 p.m., the meeting was adjourned, to reconvene on Friday, November 5, 1999.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: Vaccines and Related Biological Products Advisory Committee
Session No. 5

Before: DHHS/FDA/PHS/CBER

Date: November 4, 1999

Place: Bethesda, MD

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