Valitus hallinto-oikeudelle Helsingin ja Uudenmaan sairaanhoitopiirin Koordinoivan eettisen toimikunnan ratkaisusta § 105 07.04.2009 (liitteenä)

Ratkaisu liitteenä (kaksi sivua varsinaisen valituksen jälkeen). Tietoa FinOM-tutkimuksen korvatulehduksia lisäävästä vaikutuksesta (serotype replacement) liitteenä.

Valittajan nimi ja postiosoite:

[redacted]

Päätös johon muutosta haetaan

Päätöksessä on katsottu, että GlaxoSmithKlinen toimeksiannosta Terveyden ja hyvinvoinnin laitoksen ja kuntien kunnallisissa lastenneuvoloissa tekemän rokotetutkimuksen (FinIP-tutkimus) eettinen arviointi (tutkimuksesta vastaavan henkilön ja eettisen toimikunnan toimesta) olisi julkisuuslain mukaan salassapidettävää tietoa yksityisen liike- ja ammattisalaisuuden vuoksi.

Päätöksessä on katsottu, että kyse ei olisi tiedoista, jotka sisältävät tietoja muusta vastaavasta yksityisen elinkeinotoimintaa koskevasta seikasta ja tiedon antaminen aiheuttaisi elinkeinonharjoittajalle taloudellista vahinkoa, ja että kyse ei olisi kuluttajien terveyden tai ympäristön terveellisyyden suojaamiseksi tai toiminnasta haittaa kärsivien oikeuksien valvomiseksi merkityksellisistä tiedoista tai elinkeinonharjoittajan velvollisuuksia ja niiden hoitamista koskevista tiedoista.

Muutoksenhaku

Päätökseen haetaan muutosta sekä tutkimuksesta vastaavan henkilön eettisen arvion julkisuutta koskevan ratkaisun osalta että lausunnoista / pöytäkirjanotteita koskevalta osaltaan.

Päätökseen vaaditaan muutosta lausuntojen/pöytäkirjanotteiden osalta siten, että lausunnot/pöytäkirjanotteet ovat kokonaisuudessaan julkisia asiakirjoja.

Eettisen arvion osalta vaaditaan asiakirjasta tiedonsaantia ensisijaisesti kokonaisuudessaan ja toissijaisesti ne kohdat peittäen jotka ovat julkisuuslain mukaan sellaisia joita ei voida luovuttaa.

Tarkemmat perustelut vaatimuksiin ilmenevät jäljempää.

Vireillepanoajan alkaminen

Vireillepanoajan suhteen lienee pöytäkirjanotteen (liite) päiväyksestä 14.4.2009 kulunutta seitsemää päivää pidettävä päätöksen tiedoksisaantiajankohtana, koska päätös on postitettu tavallisena kirjeenä.

Lainkohta:

Julkisuuslain mukainen salassapitoperuste johon ratkaisussa vedotaan, kuuluu:

"20) asiakirjat, jotka sisältävät tietoja yksityisestä liike- tai ammattisalaisuudesta, samoin kuin sellaiset asiakirjat, jotka sisältävät tietoja muusta vastaavasta yksityisen elinkeinotoimintaa koskevasta seikasta, jos tiedon antaminen niistä aiheuttaisi elinkeinonharjoittajalle taloudellista vahinkoa, ja kysymys ei ole kuluttajien terveyden tai ympäristön terveellisyyden suojaamiseksi tai toiminnasta haittaa kärsivien oikeuksien valvomiseksi merkityksellisistä tiedoista tai elinkeinonharjoittajan velvollisuuksia ja niiden hoitamista koskevista tiedoista;"

Muutoksenhaun tarkemmat perusteet

Koordinoivan eettisen toimikunnan ratkaisu on virheellinen sekä menettelytavoiltaan (julkisuusalain määräaikojen täyttämättä jättäminen) että perusteiltaan.

Määräajan täyttäminen

Asiakirjapyyntö on esitetty 25.2.2009, mutta vastaus on päivätty vasta 14.4.2009. Ratkaisu on viivästynyt vastauksen perusteella siksi, että asia on jätetty tosiasiassa tutkimuksen toimeksiantajan lääkeyhtiö GlaxoSmithKlinen ratkaistavaksi, toisin kuin julkisuuslaki edellyttäisi – kysymyksen ratkaisee se viranomainen, jonka hallussa asiakirja on. Eettinen toimikunta kertoo vastauksessaan kysyneensä asiasta lääkeyhtiö GlaxoSmithKlinelta, ja saaneensa ”lausunnon 27.3.2009, jossa ei anneta lupaa salassa pidettävien asiakirjojen antamiseen”, myöntäen siten antaneensa asiakirjapyynnön tietojen julkisuuskysymyksen ratkaisemisen tosiasiassa lääkeyhtiölle.

Perusteet

Ratkaisun perusteluissa kirjoitetaan mm: ”Yksityisen liike- ja ammattisalaisuuden suojaamiseksi määrätty salassapitovelvoite on ehdoton ja salassa pidettäviä tietoja voidaan antaa vain sen suostumuksella, jonka hyväksi salassapitovelvollisuus on säädetty.” Perustelu on tässä kohdassa virheellinen: velvoite ei ole ehdoton, vaan ehdollinen, salassapitovelvoitetta ei ole tapauksessa jossa on kyse ”kuluttajien terveyden tai ympäristön terveellisyyden suojaamiseksi tai toiminnasta haittaa kärsivien oikeuksien valvomiseksi merkityksellisistä tiedoista tai elinkeinonharjoittajan velvollisuuksia ja niiden hoitamista koskevista tiedoista”. Tässä tapauksessa (kunnallisissa lastenneuvoloissa n. 90 000 lapsella, n. 80 prosentissa kunnista) kyse on sekä ympäristön terveellisyyden suojaamiseksi merkityksellisistä tiedoista että elinkeinonharjoittajan velvollisuuksien (mm. lääketutkimuksia koskeva lainsäädäntö: tutkimuslaki, lääkelaki) noudattamista koskevista tiedoista.

Ratkaisua perustellaan myös mm. pörssiyhtiö GlaxoSmithKlinen velvollisuuksilla kansainvälisen pörssitiedotuksen suhteen. Kansainväliset pörssiyhtiön tiedottamisvelvollisuutta koskevat säännökset eivät luonnollisestikaan ohita Suomen julkisuuslakia. Käytännössä GlaxoSmithKlinen luonnollisesti joutuu harkitsemaan erikseen, mitä pörssisäännöt edellyttävät tiedotukselta tutkimusten myötä julkisuuslainsäädännännön mukaan julkisiksi tulevien tietojen osalta.

Ratkaisua perustellaan myös sillä, että tiedon antaminen asiakirjoista aiheuttaisi elinkeinonharjoittajalle taloudellista vahinkoa. Näkemystä vahingon aiheuttamisesta ei perustella muulla kuin kriittistä tarkastelua kestämättömällä viittauksella pörssin tiedotussääntöihin.

Kun otetaan huomioon lapsilla tehtävien lääketieteellisten tutkimuksen eettisen arvioinnin tarkoitus, päätös perusteluineen tuntuu eriskummalliselta. Miten kunnallisissa lastenneuvoloissa tehtävän tutkimuksen eettisen arvion julkistaminen aiheuttaisi tutkimuksen toimeksiantajalle vahinkoa? Voiko tällainen päivänvaloa kestämätön tutkimuksen eettinen arviointi osoittaa että tutkimuksen asiat ovat eettisesti kestävällä pohjalla? Ratkaisua voisi verrata vaikkapa siihen, että jollakin toisella alalla toimiva yhtiö teettäisi arvioinnin lapsityövoiman käytöstä alihankkijoidensa toiminnassa, mutta päättäisi olla julkistamatta arvioinnin tuloksia perusteena että julkistaminen voisi aiheuttaa taloudellista vahinkoa yhtiölle.

Aiempien mm. Terveyden ja hyvinvoinnin laitoksen edeltäjän Kansanterveyslaitoksen tekemien rokotetutkimusten (vastuuhenkilönä Terhi Kilpi kuten tässä FinIP-tutkimuksessakin) perusteella on tiedossa, että rokote voi lisätä tiettyjen bakteerien aiheuttamia korvatulehduksia, näin on havaittu aiemmissa tutkimuksissa tapahtuneen. (USA:n lääkevalvontaviraston FDA:n kuuleminen / FinOM trial, Terhi Kilpi, http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3854t1.htm – ote liitteenä) Tässä tutkimuksessa odotetaan rokotteen vaikuttavan rokotetun lisäksi myös ympäristön bakteeritilanteeseen. Niinpä on hyvin mahdollista, että rokote lisää myös ympäristössä tiettyjen bakteerien aiheuttamia infektioita (mm. korvatulehduksia) ja näin ollen kyse on lain mukaisista "kuluttajien terveyden tai ympäristön terveellisyyden suojaamiseksi tai toiminnasta haittaa kärsivien oikeuksien valvomiseksi merkityksellisistä tiedoista."

Elinkeinonharjoittajan velvollisuuksia koskevista tiedoista on myös kysymys. Velvollisuuksia asettaa mm. laki lääketieteellisistä tutkimuksista (tutkimuslaki) ja lisäksi Maailman lääkäriliiton Helsingin julistuksen katsotaan velvoittavan tutkimuksen tekijöitä mm. kertomaan tutkimuksen riskeistä jne. Myös lääkelaki asettaa velvollisuuksia elinkeinonharjoittajan lukuun tässä tapauksessa toimiville Terveyden ja hyvinvoinnin laitoksen ja kuntien henkilöille.

Koordinoiva eettinen toimikunta § 105 07.04.2009

2/13/03/00/09 MUUT ASIAT: JYRKI KUOPPALAN ASIAKIRJAPYYNTÖ KOSKIEN TUTKIMUSTA 375/13/03/00/08

2/13/03/00/2009

TMKE10 § 105

JYRKI KUOPPALAN ASIAKIRJAPYYNTÖ KOSKIEN TUTKIMUSTA 375/13/03/00/08

Esittelijä LT Katia Käyhkö

Kuvaus

Rokotusinfo ry:n puheenjohtaja Jyrki Kuoppala on 25.2.2009 pyytänyt HUS:n Koordinoivalta eettiseltä toimikunnalta asiakirjakopioita sen 4.11.2008 käsittelemästä lääketieteellisestä tutkimuksesta, jossa tutkimuksen toimeksiantaja ja rahoittaja on GlaxoSmithKline (HUS:n Dnro 375/13/03/00/08). Kopioita on pyydetty toimikunnan tutkimussuunnitelmasta antamista lausunnoista/pöytäkirjanotteista (4 kpl: 4.11.2008, 15.1.2009, 3.2.2009 ja 24.2.2009) sekä tutkimuksesta vastaavan eettisestä arviosta. Kyseiset asiakirjat on merkitty salassa pidettäviksi julkisuuslain 24 § 1 momentin 20-kohdan perusteella.

Julkisuuslain (621/1999) 24 §:n 1 momentin 20-kohdan mukaan salassa pidettäviä ovat asiakirjat, jotka sisältävät tietoja yksityisestä liike- tai ammattisalaisuudesta, samoin kuin sellaiset asiakirjat, jotka sisältävät tietoja muusta vastaavasta yksityisen elinkeinotoimintaa koskevasta seikasta, jos tiedon antaminen niistä aiheuttaisi elinkeinonharjoittajalle taloudellista vahinkoa, ja kysymys ei ole kuluttajien terveyden tai ympäristön terveellisyyden suojaamiseksi tai toiminnasta haittaa kärsivien oikeuksien valvomiseksi merkityksellisistä tiedoista tai elinkeinonharjoittajan velvollisuuksia ja niiden hoitamista koskevista tiedoista.

Yksityisen liike- ja ammattisalaisuuden suojaamiseksi määrätty salassapitovelvoite on ehdoton ja salassa pidettäviä tietoja voidaan antaa vain sen suostumuksella, jonka hyväksi salassapitovelvollisuus on säädetty. Muuta elinkeinotoimintaa koskevasta seikasta tietoja voidaan antaa, jos tietojen antamisesta ei aiheudu elinkeinonharjoittajalle taloudellista vahinkoa. Se viranomaisen, jonka hallussa asiakirjat ovat, on ennen tietojen antamisesta päättämistä arvioitava, aiheuttaako tietojen antaminen elinkeinonharjoittajalle taloudellista vahinkoa. Kokouksessaan 17.3.2009 eettinen toimikunta päätti asian selvittämiseksi kuulla tutkimuksen toimeksiantajaa. Toimeksiantajalta on nyt saapunut vastaus lausuntopyyntöön. GlaxoSmithKline ei lausunnossaan puolla asiakirjojen antamista Kuoppalalle.

GlaxoSmithKline on kansainvälinen pörssissä noteerattu yhtiö. Pörssiyhtiöiden tiedottamisvelvoitteesta on olemassa erilliset säännökset. Tietojen antaminen pörssiyhtiön tuotekehitys- tai tutkimushankkeen etenemisestä tiedotusvelvollisuuden ulkopuolella voi aiheuttaa elinkeinonharjoittajalle vahinkoa. Jyrki Kuoppala ei asiakirjapyynnössään ole ilmoittanut pyytämilleen asiakirjoille sellaista käyttötarkoitusta, että tiedot voitaisiin antaa salassapitosäännöksistä huolimatta.

Päätösesitys

Toimikunta on saanut asiassa tutkimuksen toimeksiantajan lausunnon 27.3.2009, jossa ei anneta lupaa salassa pidettävien asiakirjojen antamiseen. Eettinen toimikunta päättänee olla antamatta tietoa Kuoppalan pyytämistä

asiakirjoista, koska ne sisältävät tietoja yksityisestä liike- tai ammattisalaisuudesta sekä vastaavasta yksityisen elinkeinotoimintaa koskevasta seikasta, kun tiedon antaminen niistä aiheuttaisi elinkeinonharjoittajalle taloudellista vahinkoa.

Päätös

Eettinen toimikunta päättää olla antamatta tietoa Jyrki Kuoppalan pyytämistä asiakirjoista, koska ne sisältävät tietoja yksityisestä liike- tai ammattisalaisuudesta sekä vastaavasta yksityisen elinkeinotoimintaa koskevasta seikasta, kun tiedon antaminen niistä aiheuttaisi elinkeinonharjoittajalle taloudellista vahinkoa.

Lisätietoja

Katia Käyhkö p. 050 339 2688

Otteen tarkastamattomasta pöytäkirjasta oikeaksi todistaa

Helsingissä 14.4.2009

[redacted]

Lähetetty tiedoksi

14.4.2009

Jakelu

Kuoppala Jyrki, Rokotusinfo ry:n puheenjohtaja
Knudsen Petteri, Lääketieteellinen johtaja, GlaxoSmithKline
Lindqvist Ari, ylilääkäri
Sorsa Pirjo, hallintolakimies

Dr. Kilpi, welcome.

DR. KILPI: Good morning. I'm going to present the main efficacy results of the Finnish otitis media vaccine trial that evaluated the efficacy of two seven-valent pneumococcal conjugate vaccine for prevention of acute otitis media due to vaccine serotypes in children less than two years of age.

And this study was conducted in the Tampere area in Finland, and the clinical phase started in December '95 and ended in March '99, and during this time, we had almost 2,500 children were enrolled in the study. This is approximately 55 percent of the birth cohort in the area.

And all of these children were randomized to receive either one of the two pneumococcal conjugate vaccines used in the study, the PncCRM vaccine labeled, licensed as Prevenar or the PncOMPC vaccine or the control vaccine that was Hepatitis B vaccine in our study.

And the children received these vaccines at the age of two, four, six, and 12 months. They were followed in study clinic setting from two months to 24 months of age, and during the follow-up every effort was made to have all respiratory infections according to these children requiring medical attention evaluated and treated at the study clinics by our study physicians.

This trial was specifically designed to study otitis media, and therefore, we needed a definition for acute otitis media, and we defined that there has to be symptoms of acute infection and signs of inflammation in the middle ear.

And whenever acute otitis media meeting this definition was diagnosed at the study clinic by our study physician, myringotomy was performed and middle ear fluid aspirated for bacterial culture, pneumococcal serotyping when appropriate, and pneyumolysin PCR.

Otitis media is a condition that tends to recur in a proportion of individuals over and over again, and we, therefore, wanted to analyze the vaccine efficacy by all AOM episodes rather than just the first ones, and we, therefore, needed a definition for an episode.

And we defined that it starts at diagnosis and lasts for 30 days. And these were the endpoints we looked at, and these were defined in the protocol and in the analysis plan. The primary endpoint was all AOM episodes due to vaccine

serotypes.

The secondary was first and subsequent AOM episodes due to vaccine serotypes, and we also looked at all pneumococcal AOM episodes, at all AOM episodes, and recurrent AOM.

We have late also performed some additional analysis, looked at endpoints of special interest, namely AOM episodes due to vaccine related serotypes, due to serotypes unrelated to vaccine types, and also calculated the vaccine efficacy against AOM episodes due to individual pneumococcal serotypes.

And from now on, I will present the results for the PncCRM group of this study as compared to the control group and forget about the third arm since this is the vaccine we're talking about today, and to start with, I hope this slide will demonstrate to you that our trial was very successfully conducted.

Of the 1,662 children enrolled in these two groups, as many as 1,580 completed the trial without critical protocol violations. That is, 95 percent of the children originally randomized. So we feel pretty comfortable with the results.

And now to the results. During the protocol follow-up period that lasted from 6.5 to 24 months of age, there were 107 AOM episodes due to the vaccine serotypes in the PncCRM group as compared to 250 episodes in the control group.

And this means that the vaccine efficacy against the primary endpoint, all AOM episodes due to vaccine serotype was 57 percent, and this efficacy was statistically significant as indicated by the confidence interval here.

And to the secondary analysis, the vaccine efficacy against AOM, first episodes of AOM due to vaccine serotypes was 52 percent, and the vaccine efficacy in the subgroup of children who had already had one AOM caused by the vaccine serotypes was 48 percent. So the vaccine does provide protection even if a tad failed one.

And this is a summary of the main efficacy results, AOM, vaccine efficacy against AOM due to vaccine serotype, 57 percent; against culture confirmed pneumococcal AOM, 34 percent; against pneumococcal AOM confirmed by either culture or PCR, analyzing PCR or both, 20 percent. These are all statistically significant. Against any AOM, six percent, and recurrent AOM, 16 percent. The latter two failed to reach statistical significance in our study.

And these were the analyses for the protocol analysis, and this is the same for the intention to treat analysis and for the intention to treat follow-up period that started already at two months of age.

And as you can see, the results are very similar to the protocol analysis. What may attract attention in these efficacy results is the different efficacy the vaccine provided against culture confirmed pneumococcal AOM as compared to pneumococcal AOM confirmed by either culture or PCR, and therefore, we have looked at this issue a bit more closely and found that the vaccine does not provide any protection against chemical culture, negative but PCR positive AOM, and this explains the difference between these two entities.

And since the PCR method we used in our study was quantitative or perhaps more precisely semi-quantitative, we have also been able to look at the PCR counts in the pneumococcal culture negative cases of AOM as compared to the Pnc culture positive cases and found that the PCR counts are considerably higher if the pneumococcal culture is positive than if it's negative.

So whatever the significance of PCR positivity in the pneumococcal culture negative cases of AOM is, it certainly does not seem to be a sign of active pneumococcal disease.

The design of the FinOM vaccine trial allowed us to characterize the vaccine efficacy a bit further because we had the culture results from each even of otitis media and we had the serotyping results. And one of the things we were interested in was if the vaccine provided the same kind of efficacy or different kinds of efficacy against AOM caused by individual vaccine serotypes, and this is what we found.

The efficacy against AOM caused by 6B was excellent. The point estimate is 84 percent. It's good against AOM caused by 23F and 14 point estimates, from 60 to 70 percent, but rather modest for AOM caused by Type 19F, point estimate being only 25 percent.

When we designed the trial and decided to have AOM caused by the vaccine serotypes as our primary endpoint, we knew that we could anticipate that the vaccine might protect also against other than vaccine, against AOM caused by other than vaccine serotypes only, and that is the relative serotypes to the vaccine serotypes, and therefore, we have also wanted to look at this and we found, indeed, that there were 41 AOM episodes caused by the vaccine related serotypes in the PncCRM group as compared to 84 episodes in the control group, and this means that the vaccine efficacy against AOM due to the vaccine related serotypes is 51 percent, which is almost as good as the efficacy against AOM caused by the vaccine serotypes themselves.

However, when we come to the other serotypes, the non-vaccine, non-vaccine related serotypes, we see in excess of 30 episodes caused by these serotypes in the PncCRM group as compared to the control group, which translates into a negative efficacy of minus 33 percent in the vaccine group as compared to the control group, and this difference almost reached statistical significance.

However, the bottom line is that the vaccine provides protection against any culture confirmed pneumococcal AOM and reduces it by 34 percent.

And this is now vaccine efficacy against AOM caused by the two most common cross-reactive serotypes, 6A where the point estimate is 57 percent and 19A where the point estimate, 34 percent, actually is even a little higher than for the vaccine serotype 19F itself.

So conclusions from this trial follow-up part are the the PncCRM vaccine is efficacious against culture confirmed vaccine serotype specific, active otitis media, culture confirmed AOM due to the vaccine related serotypes, and culture confirmed pneumococcal AOM.

And now I will move on to the extended follow-up. We have recently collected additional information on the children enrolled in the PncCRM and control groups to assess the long-term effects of the PncCRM vaccine on pneumococcal carriage, antibody persistence, and surgery due to otitis media in the routine practice when those children had completed the trial follow-up.

And I will now present the results for this category as specifically the effect of the vaccine on the incidence of tympanostomy tube placements up to four to five years of age.

I will also briefly present some results for the other two categories.

And this extended follow-up was carried out by inviting the children to a single follow-up visit in spring 2001 when they were at the age of four to five years. And we invited altogether 1,490 children. They represent 90 percent of the original study population, and these were the children who had completed the ITT follow-up and who were still living in the Tampere area.

And 756 of these children followed the invitation and were evaluated at the study clinic in spring 2001, and since

these children only represent 45 percent of the original study population, we have also collected information on the tympanostomy tube placement of these children, these 1,490 children to be able to feel comfortable with our tympanostomy tube results.

And I will now show you what kind of data we have available on the tympanostomy tube placements of these children and for which categories of children we have this date.

So, first, the analysis populations. Initially all children were followed from two to 24 months of age in the study clinic. So we had 1,662 children at the beginning and 65 of them dropped out during the trial. So at the end we had 1,597 children, and of these, 107 had moved out or the Tampere area after they completed the follow-up in the trial setting.

So we had, 1,490 children still living in the area, and these children constitute the eligible children, the analysis' population two.

Then we have this subgroup of children, the 756 fully evaluated children, and they constitute the analyst population one, and for this part of children, we have completed tympanostomy data available, and for this part of children, we have the hospital tympanostomy tube data available.

And tympanostomy tube placement in the FinOM follow-up study were ascertained in the following way. For the fully evaluated children, we could ask the parents if the child had had tubes placed after completing the trial follow-up and then confirm the parents' answers by reviewing the hospital records collected from the area hospitals and by reviewing the medical records requested from private physicians.

And it turns out that 78 percent of the tympanostomy tube placement had been performed in public sector hospitals and 22 percent in private medical centers.

For the eligible children we had the hospital records from the area hospitals which are likely to represent approximately 80 percent of the tympanostomy tube placement performed in these children after they completed the trial follow-up.

And before I go to the results, I think I need to explain to you what kind of practices were followed during the vaccine trial and after it when the children returned to normal life, to the real life situation.

During the trial, tube placement, if considered indicated, was included in the study services. They were almost exclusively performed at the Tampere University hospitals. They were free of charge to the patients, and the hospital guaranteed access to treatment within four to five weeks of referral.

When the trial follow-up was over, the children returned to normal life, and in the real life situation in Finland if tube placement is considered indicated, there are two options, two possibilities to have it performed. It can either be done in public hospitals where the charge is nominal, but waiting time can be from three to four months, or it can be performed in private medical centers that charge ten times that of their public sector charge, but there is no waiting time.

And so principally, the indications for tympanostomy tube placement were the same during the vaccine trial and after the trial when the children had returned to the normal life situation, but access to treatment became definitely more difficult when the trial follow-up was over due to the reasons here.

And this makes plain why the incidence of tympanostomy tube placements in the FinOM children during the vaccine trial follow-up was considerably higher than what it is in the children of the same age in Finland in general.

And it also makes plain why this incidence of tympanostomy tube placement dramatically dropped when they returned to a normal life situation. So it appears that milder cases of recurrent AOM and otitis media with effusion were treated with tympanostomy tube placement during the trial and after it, and this makes plain why the effect of the vaccine on the incidence of tube placement was different here from what it was here.

Okay. Now I'll go to the results, and we'll just remind you that I'm going to present them for the full evaluated children analysis population one and for the all eligible children analysis population two.

And these are the tympanostomy tube placements in the fully evaluated children. During the trial follow-up from two months to two years of age, 20.3 percent of the children in the PncCRM group as compared to 23.8 percent of the children in the control group had tympanostomy tubes place, and the incidence rate of events is here.

So the difference between the vaccine group and the control group is 12 percent, and this is not statistically significant.

However, when the normal life situation started during the period from two years to four to five years, only 8.2

percent of the children in the PncCRM group as compared to 13 percent of the children in the control group had a tympanostomy tube placement. The incidence is shown here, and the conclusion is that the vaccine reduced tympanostomy tube placements during this age period of time by 39 percent, and this difference is statistically significant.

And since we have only 45 percent of the original study population in these fully evaluated children, it was, of course, important to see if the results are the same for all eligible children for which we had the public sector hospital data available. And so now only the tympanostomy tube placements performed in the public hospitals are included in this slide.

And here the difference during the trial follow-up is even smaller. It's only four percent, but, again, during the normal life follow-up from two years to four to five years of age we see a reduction of 44 percent in the incidence of tympanostomy tube placements in the PncCRM group as compared to the control group.

And even the lower limit of the 95 percent confidence interval is as high as 19 percent.

Now, this shows the same thing for the fully evaluated children graphically. This is the cumulated hazard for tympanostomy tube placement, and as you can see, there is practically no difference during the trial follow-up up to 24 months of age, but after, as soon as they return to normal life, the curves start to part and continue to do so.

So there is no sign of waning efficacy here. And this is the same thing for all eligible children, and again, the same pattern.

I will now show briefly kinetics of antibody concentrations for three of the most serotypes causing AOM in our study, and I think that these curves are beautifully consistent with the persisting efficacy I have just demonstrated.

This is the antibody concentrations for 23F, and as you can see, the level is the same at the age of 24 months and then at the age of four to five years.

For serotypes 19F and 6B, the antibody levels even seem to increase a little.

And this is data collected at the follow-up visit in spring 2001. We asked the parents if the child has had AOM after 24 months of age, and according to the parents of the children who received the PncCRM vaccines, 67 percent of these children had had AOM after completing the trial follow-up as compared to 72.7 percent of the children in the control group.

At the visit, 11.4 children in the PncCRM group as compared to 12.5 percent in the control group had middle ear

abnormalities, and 8.5 percent of the children carried vaccine serotypes as compared to 13.6 percent of the children in the control group, and this last differences is statistically significant.

So these last data is consistent with the conclusions that PncCRM reduces tube placement due to otitis media, and that the vaccine efficacy against otitis media persists for years.

Thank you.

CHAIRMAN DAUM: Thank you very much, Dr. Kilpi.

We have a few moments for clarifying questions. Dr. Griffin.

DR. GRIFFIN: After the study was completed, did the parents and the physicians know who had received vaccine and who hadn't? I mean was the blind broken and they were informed as to whether they had been immunized?

DR. KILPI: Yes. The code was broken in August '99, and the parents were informed about the vaccine their child had received in October '99, and so I guess you are wondering if this fact may have affected the results we received after the completion of the trial, and we looked at this.

DR. GRIFFIN: You just wondered whether physicians say, "Oh, well, they were vaccinated. So they wouldn't need this"?

DR. KILPI: Yes, yes, and that's why we have looked at the incidence.

Yes, because many children completed the trial follow-up long before the code was open, some of them even had two years of follow-up after the code was revealed to the parents. So we looked at the incidence of tube placements after the completion of trial follow-up, but before unblinding, and this is the incidence in the PncCRM group as compared to the control group, and this is the total.

And this is for fully evaluated children and this is for all eligible children. So I think there is no sign that unblinding would have affected the results.

CHAIRMAN DAUM: Thank you.

Dr. Diaz, then Dr. Katz, and Dr. Schwartz.

DR. DIAZ: Dr. Griffin asked my question.

CHAIRMAN DAUM: Dr. Katz, please.

DR. KATZ: On the schedule of both groups, were they also receiving Haemophilus Influenza B conjugate vaccine at the same time? I don't mean necessarily the same visit, but this was part of their routine?

DR. KILPI: Yes, yes. The concomitantly given vaccine was also DTP Hib combination that they received at the age of two, four, six -- of six months, and we used two different DTP Hib combination vaccines.

DR. KATZ: I guess I wondered why you picked Hepatitis B as the control vaccine. What was the motivation for that?

DR. KILPI: Well, it's not included in the routine program in Finland. It's only recommended for risk groups, and it seemed to be the right thing to do to offer something to the control group also, something beneficial.

CHAIRMAN DAUM: Dr. Schwartz and Dr. Overturf and Stephens.

DR. SCHWARTZ: I'm confused or at least I don't understand.

CHAIRMAN DAUM: Turn you mic on. You push that button on the base.

DR. SCHWARTZ: Yes, sorry.

When you did tympanocentesis in that group of patients, whether they were on control or on the study vaccine, was the tympanocentesis 80 percent of all episodes or as close as you could get to every single episode on the study trial or after the first tympanocentesis that yielded a pneumococcal serotype of any serotype, then that child did not have to undergo further tympanocentesis and yet remain on the study?

DR. KILPI: No. It was the first one, in the first way. So whenever they had AOM diagnosed, myringotomy actually was the procedure we used. It made a small hole and suction. So it was performed every time AOM was diagnosed, at every single visit.

Of course, this was not 100 percent. It was saying from 93 percent of the visits when AOM was diagnosed.

DR. SCHWARTZ: So some children could have undergone six procedures or five procedures during this study?

DR. KILPI: I'm afraid so.

CHAIRMAN DAUM: Thank you.

Dr. Overturf and Dr. Stephens.

DR. OVERTURF: I wondered on the organisms that came from both the vaccine related serotypes as well as the organisms from the non-vaccine related serotypes whether you had any antibiotic susceptibility data on either one of those groups as compared perhaps to the serotype from the vaccine.

Do you have that data?

DR. KILPI: We do. We looked at -- what we have in the database is the data on penicillin resistance, but the resistance situation in Finland is very different from that in the U.S. So that almost all of them were susceptible to penicillin.

However, if they were not susceptible they were usually or I think they were exclusively vaccine serotypes.

CHAIRMAN DAUM: Thank you.

Dr. Stephens and then Dr. Decker.

DR. STEPHENS: Two questions. One had to do with the PCR count data. Can you give us a better understanding of that in terms of organisms per mL, presumably in terms of those counts.

DR. KILPI: I'm afraid I can't. As I told you, this method is semi-quantitative. We have now developed also using a better PCR method that allows quantification in a better way. This was just to demonstrate that obviously this huge difference tells us that it is the PCR negative case -- PCR positive, culture negative cases are something different from the culture positive case.

DR. STEPHENS: Okay. Can you also provide any information regarding the serotype replacement issue? That is, is there a difference between non-vaccine serotypes?

You gave us the data that there was a significant difference between vaccine serotypes. Is there an increase in non-vaccine serotypes in terms of carriage?

DR. KILPI: In terms of carriage? Yeah, well, I have some carriage data here.

(Pause in proceedings.)

DR. KILPI: So, well, this is first to show that the vaccine does not have effect on the overall carriage of pneumococcus. This is the other carriage figures at the age of 12 months, 18 months, and four to five years in the PncCRM group as compared to the control group. So always it's approximately the same proportion of children that are carriers.

And then this shows the carriage rates at 12 months of age, and actually there we did not see any statistical differences in these three categories. So there was perhaps a small reduction of the carriage of vaccine serotypes, but this is not statistically significant, and these are also pretty much the same.

This is different from the rate that is obtained in the developing countries. So the effect of the vaccine seems to be different. The effect of the vaccine on carriage seems to be different in developing country situations than in an industrialized country perhaps.

And here we have the carriage rates at the age of 18 months, and there is clear reduction in the carriage of vaccine serotypes. Cross-reactive serotypes are approximately even, and there is replacement by the non-vaccine related serotypes.

And when we come to the age of four to five years, again, we see the reduction in the carriage cell vaccine serotypes, and this time the situation for the other serotypes is even, but there is a small increase of the carriage of the cross-reactive serotypes in the PncCRM group as compared to the control group. However, these differences are not statistically significant.

CHAIRMAN DAUM: Thank you.

Dr. Decker.

DR. DECKER: No questions.

CHAIRMAN DAUM: Dr. Whitley.

DR. WHITLEY: This is an obvious question, and logically antibiotic usage would be lower in the vaccinated compared to the control population. Do you have data to support that logical assumption?

And specifically what I'm trying to get at is was there extraneous antibiotic usage in the vaccinated compared to the non-vaccinated group?

DR. KILPI: I don't have any slides to support that, but the number of antimicrobial prescriptions in the vaccine group was lower than in the control group, and I think it is covered in the FDA presentation.

CHAIRMAN DAUM: Okay. We have time for two more comments. Dr. Faggett.

DR. FAGGETT: Thank you. This is valuable clinical data.

Question number one, do you have national health insurance in Finland?

And Part 2 of my question: what were the criteria for tube placement? It would appear that with decreased costs and increased access that might impact on decisions to have the tube placement.

DR. KILPI: Yes, we do have national health insurance in Finland, and this basically means that the public sector is free of charge or the charge is only nominal, and for the private care, the children get reimbursed for the treatment.

So part of the sum is paid back, but anyway, the cost is considerably more to the parents than what would be in the public sector.

And the indications for tube placement, the recommended indications, I think, are pretty much the same as in the U.S. It's recurrent AOM, three to six episodes per six months or persistent otitis media with effusion.

But of course, as everyone knows, I think, that in a trial situation when it is really followed that this happens, it's different than if parents and doctors make individual decisions based on the waiting list and the financial situation of the family.

CHAIRMAN DAUM: And the age.

DR. KILPI: Yes.

CHAIRMAN DAUM: Dr. Glode.

DR. GLODE: I just wanted to clarify the original entry criteria. I know I read in the briefing materials that the public health nurse gave the vaccine and enrolled the patient in the study initially at two months of age or whatever; is that correct that that was generally done by public health nurses?

DR. KILPI: Well, they are public health nurses by training.

DR. GLODE: Yes.

DR. KILPI: They were trial staff. It's the policy in Finland that nurses vaccinate, and they were hired -- they were part of our staff team. So it was not their normal public health nurses, but it was a vaccinator we had hired for the trial.

DR. GLODE: Okay, and they knew which vaccine they were giving?

DR. KILPI: No. No, they didn't.

DR. GLODE: Okay. They were blinded.

DR. KILPI: Well, the vaccines were letter coded, and there was six letter codes for the three vaccines, and the vaccinator knew naturally which letter code the child received, and they were, therefore, kept separate from the other staff so that the staff didn't even know which letter code was assigned to each child, and this was never recorded anywhere.

DR. GLODE: Okay. Thank you.

CHAIRMAN DAUM: I'm going to take prerogative for the last question.

You showed some antibody data between the Prevnar vaccinees and the hepatitis vaccinees for several of the serotypes. Do you have similar data for Type 19F?

DR. KILPI: I showed for 19F.

CHAIRMAN DAUM: Did I miss it?

DR. KILPI: Yeah, it was --

CHAIRMAN DAUM: I'm sorry.

DR. KILPI: It was increasing also.

There.

CHAIRMAN DAUM: So I guess the question is then in light of the relative poor efficacy against that serotype, what do these kinds of data mean in terms of inferring protection?

DR. KILPI: Well, especially when it comes to 19F, it's very, very difficult to make any conclusions from the antibody concentrations and try to correlate to the efficacy. Obviously, these are antibody concentrations that look rather

good anyway. Not a very good efficacy can be reached against otitis media.

CHAIRMAN DAUM: Thank you very much.

I think we now must move on to the next part of the sponsor's presentation, which would be Steve Black again to tell us about the Kaiser trial efficacy.

Thank you very much, Dr. Kilpi.

DR. BLACK: Thank you, Dr. Daum and everyone.