Prevention of Recurrent AOM with Pneumococcal Conjugate Vaccines

Ron Dagan

My role is to present you the role of Pneumococcal Conjugate Vaccines (PCV) in the prevention of recurrent acute otitis media (RAOM). I am not going to mention about the role of this vaccines to prevent otitis in general, I was asked to really concentrate on whether we can reduce the RAOM problem with conjugate vaccine. As I am going to show you, the answer is not simple, and the future will tell us a lot about it.

We just have to remember, again, that all pneumococci reside mainly in the nasopharynx, some in the oral pharynx, but this is the place from where they can spread, either because mucosal infection, such as otitis, as we are talking about now, they can invade bloodstream also, and cause various infections, but very importantly, they also spread from one person to the other, from one nasopharynx to the another, and if we're talking about vaccines, they will have to have an effect on all of those.

I will concentrate on the effect of the vaccine on otitis, or RAOM, but at the same time I will have to take care what the vaccine is doing to the nasopharynx and the spread to the organisms.

There are several studies - and even more now - that show the same thing, although there are different investigators, different vaccines, different sites, different ages. All of them show very clearly that if you give conjugate vaccine to children you are able to reduce the carriage of the pneumococci serotypes that is in the vaccine. So if you give a 7-Valent vaccine, you can reduce the serotypes in the nasopharynx (the serotypes included in the 7-Valent vaccine).

Since antibiotics resistance is mainly concentrated on these 5 serotypes worldwide: 6B, 9V, 14, 19F, 23F; these 5 serotypes are mainly the serotypes that represent penicillin resistance, macrolide resistance and multi-resistance, and they are all included in the vaccine.

So the fact that we have a reduction in the nasopharynx of the vaccine serotypes is also accompanied by the fact that we have a reduction in the nasopharynx of those that are antibiotic-resistant. There are studies where it was looked, the vaccine reduced the carriage of antibiotics resistance to pneumococci, at the same time that they reduced the carriage of vaccine serotypes.

But a phenomenon was found, which was not expected that it is well established now, when we talk about the flora. So you reduce some of the pneumococci,

including the resistant pneumococci, but you have a replacement, with other pneumococci, and this is again very well established, and it is called replacement phenomenon, and it is very important for the understanding of what vaccines are doing to respiratory infections. But nature so far showed us that if we reduce the pneumococci, we are going to have other pneumococci, that are going up, that are not part of the serotypes of the vaccine.

Just to show you one example, from a study that O'Brien and colleagues did in Arizona (O´Brien et al, 18th ESPID, Istanbul, March 2001) in Native Americans. The control children, that did not receive the 7-Valent vaccine (Prevenar) 36% were culture-negative in the nasopharynx. From those 65% who were culture-positive, 23% had vaccine-serotypes, and the others had serotypes not in the vaccine. When you look at what happened to the vaccinated, there was a clear and highly statistically si nificant reduction in the vaccine serotypes, but a replacement with non-vaccine serotypes, and eventually you have the same carriage rate, but now with different serotypes.

This is exactly the replacement phenomenon.

Now, if you remember how otitis is, and most of you that are reading this Manual are MDs and know much better than me, how otitis media appears. Let me just remind you that it starts almost always with an upper viral respiratory infection (UVRI), and eventually, the Eustachian tube (ET) dysfunction has its role. Eventually, those two (UVRI and ET) are responsible for the invasion of bacteria to the middle ear and cause otitis media.

Now if you think that we took off some of the pneumococci but we had them replaced by other, it is very easy to see that the new colonizing pneumococci can now be the ones that are attracted into the ear, and the replacement phenomenon that we saw with the nasopharyngeal carriage, may be occurring also in otitis media.

Indeed, there are 2 studies (Eskola et al, N Engl J Med 2001;344:406-409 and the Kilpi et al study - submitted) that look very carefully into that, and these 2 studies were done in Finland - they are amazing studies. They enrolled several thousand children and they gave them either placebo or one vaccine which is conjugated with outer membrane protein of meningococcus or another vaccine that was the Prevenar. In the placebo double-blind study, they looked at them and followed them and every time they had the bulging tympanic membrane (TM) they had tympanocentesis.

This was very important, because we could learn a lot. And this is the Prevenar, this is the OMPC vaccine. Let us start with the Prevnar. When you look at the vaccine serotype, the 7-serotypes that are in the vaccine, you can see that there was a 57% protection, a reduction of 57% of otitis media that occurred by this vaccine. So, the vaccine was doing very well.

Even those who are related - say 6A when in the vaccine you have 6B is a related, 19F in the vaccine, 19A is related - even in the related in this case there was a 57% protection. But the non-vaccine serotypes, they were replacing here: 33% increase in otitis media.

With the OMPC vaccine, it was the same for vaccine serotypes, but it was not the same for the vaccine-related and the effect on the *H. influenzae* and *M. catarrhalis* and non-vaccine serotypes here, were even bigger.

Overall, what happened was the following: what we really had is that with a CRM vaccine we had a 6% reduction of the overall otitis, which is not even statistically significant, and with the other one, we had a 1% increase in otitis.

So the vaccine, in both cases, does not really reduce otitis. It only reduces specific cases of otitis, that are related to the vaccine.

Now, is this important? Are we just to throw away the vaccine and forget about it? Maybe there is something in this change, and we have to look at this.

Look what happened first, that there is indeed replacement. I a study that was done in Pittsburgh (McEllistrem et al, ICAAC, Abstr # 733) looking at what was happening with isolated otitis media, before the vaccination in the United States, and after they started to vaccinate. When you look at the vaccine serotypes, after vaccine's introduction, they are always less isolated, except for 19F, which is not very successful.

When they combine all of these together you see a re-reduction of the cases of vaccine serotypes, but an increase of cases of non-vaccine serotypes, which is only a trend here. And actually when you look here, these vaccine serotypes were almost all before 2001, and now they are approaching only half.

So this is really showing that this replacement phenomenon is starting to be seen in many places…

What we see is a reduction of the cases of the vaccine serotypes. Now, if you look at what we expect now: before vaccine, usually what we have is a lot of pneumococci, a lot of vaccine serotypes and a lot of those vaccine serotypes are antibiotic-resistant. The non-vaccine serotypes are the minority of the pneumococci, and they are non-pneumococcal and negative.

Now, since vaccine, serotypes are reducing the pneumococcal vaccine serotypes, increasing the pneumococcal non-vaccine serotypes, and increasing the non-pneumococcal acute otitis media. What we actually see also is a reduction of resistance. As I mentioned to you, this is the new otitis that is going to be seen after vaccination: less pneumococci, less antibiotic-resistant pneumococci, more non-vaccine serotypes pneumococci, more non-pneumococci and some more negative.

This is a new type of otitis media. Now the question is: is this otitis media going to be more or less related to the recurrent otitis?

And remember that before vaccination these 5 serotypes (6B,9V,14,19F,23F) were the most important ones, because the most antibiotic resistance is found in these serotypes.

We did another study (Dagan et al, JID 2000;181:1332-1339) where we had a prospective sample on almost 1,000 pneumococcal otitis media cases where we had tympanocentesis in medical history. The results were that if you did not have any otitis in the last several months, you have 44% of these 5 serotypes. But if you had more otitis before, it is becoming much more common. So these 5 serotypes (6B,9V,14,19F,23F) are the ones that cause the more RAOM.

So, it is not surprising that the vaccine is not doing much to otitis in general, but it may do something to the more severe ones. And this is what you can see in the United States at the ventilation tube insertion - it is reduced by 20% and in Finland it reduced by 40%.

So, actually the more you have problematic otitis, if you vaccinate early in life, the more you are going to see protection.

There is a recent study from the northern California about effect of Prevenar on frequent otitis media, by frequency of visits (Fireman et al, Pediatr Infect Dis J 2003;22:10-16) showing that if you look at a percentage reduction, the more the otitis is frequent, the more the protection is high.

For this, I could stop here, but there are two problems - we have to understand that we have just opened a Pandora box of problems.

This is one – usually the Dutch people bring up the problem, because they are very good observers – a study group (Veenhoven et al, Lancet 2003, in press) that is starting to look at cases with already recurrent otitis media. What happens if we give them the vaccine? Are we going now to reduce RAOM?

It is a double blind, randomized study, a lot of patients with recurrent otitis, and they gave either two doses of conjugate vaccine followed by polysaccharide, or one dose to the other children. They had control with non-pneumococcal vaccine.

And what they found is that they did not change much the carriage because they had replacement, as we have said before. As you can see, the vaccinated, if you look at the vaccine type, the vaccinated dropped the vaccine serotypes but they did not control them, while the vaccinated increased the non-vaccine serotype.

We have the same phenomenon of replacement.

But they hope they will have less infection, and they hoped to have much less in the vaccinated. But actually what they found, they had more cases in the vaccinated children, and actually these are the numbers and you can see this was statistically significant, with 30% increase of otitis, despite the fact that they decreased the vaccine serotypes.

Now you can have a lot of explanations for that, and there is a lot of speculation. But this tells you that if you vaccinate children that already have established AOM, you may not be as helpful as if you do it early, before the start process of RAOM.

Another important point, going to replacement: if there is a replacement, we hope the replacement will be less antibiotic-resistant, which will make fewer problems in treatment, we have to see what exactly are the serotypes that are going to replace.

We have another big study we did in Israel with almost 2,500 isolates in the last four years, on pneumococci from the middle ear.

The majority are vaccine serotypes, or vaccine related, or even, you see really that as others we find a lot of vaccine serotypes here, these are vaccine-related, which may be affected by the vaccine. But 20% as expected are not vaccine serotypes and we wanted to see whether these were more or less antibiotic-resistant.

The vaccine serotypes are 80% penicillin non-susceptible, very resistant. Of those, 50% are highly resistant and 27% multi-drug resistant. To go to the vaccine-related or somewhat affected by the vaccine, 73% penicillin resistant, but less high and multi-drug resistant.

If you go to those which will be the new replacements, they are much less resistance to penicillin, almost non-existent high-resistance almost non-existing multi-drug resistance.

So the good news is, replacement is going to give us much less antibiotic

resistance. The bad news is that you already have resistance. It is not free of resistance. And in fact, we find 5 new serotypes that are quite important, that are very much antibiotic resistant.

And actually when you look with molecular biology, you find that they are clonal. So we now have resistant clones, that are not of the vaccine, that persist, and already cause otitis. And these are the new candidates to cause antibiotic-resistant otitis, after the vaccination, and of course recurrent otitis media.

So, my conclusion is that PCV reduces NP carriage vaccine types and vaccine serotype-related pneumococcal serotypes, and increases the other ones. This is accompanied by reduction of antibiotic resistance among pneumococci, which is good news for prevention of recurrent acute otitis media.

However, replacement occurs in AOM not only by non-vaccine serotypes pneumococci but also by other organisms. So again, when we are talking about antibiotics, we have to understand that now we have more *H. influenzae*, more *M. catarrhalis*. Maybe antibiotics that are good for *S. pneumoniae* are not good for *H. influenzae*, so we have to think that we have perhaps to change also the antibiotic treatment, if we want to give antibiotics.

Therefore, following PCV, AOM is not largely reduced but modified. It is expected to be less protracted and easier to treat if we give the vaccine very early, because if we give it very late we are not going to make much change.

However, as I said before: questions regarding the timing for vaccination and outcome of replacement with antibiotic-resistant non-vaccine serotypes, remains to be determined.

So, what I showed you, is that there is some hope to reduce recurrent and prolonged problem, we can reduce resistance, we have a modified disease.

But I think what is clearly shown is that we only know a small part of what really happens. We have to be very careful in the future to understand what the vaccine is going to do, because the vaccine is dealing with microorganisms in the flora, which means we are going to see a lot of surprises.

Recommended reading

1. Dagan R, Givon-Lavi N, Fraser D, Lipsitch M, Siber GR, Kohberger R. Serum serotype-specific pneumococcal anticapsular immunoglobulin G concentrations after immunization with a 9-valent conjugate pneumococcal vaccine correlate with nasopharyngeal acquisition of pneumococcus. J Infect Dis. 2005 Aug 1;192(3):367-76.
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3. Dagan R. The potential effect of widespread use of pneumococcal conjugate vaccines on the practice of pediatric otolaryngology: the case of acute otitis media. Curr Opin Otolaryngol Head Neck Surg. 2004 Dec;12(6):488-94.

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