History and Development of Haemophilus Influenzae Type B Vaccine

With the relaunch of Pediatric Annals, we’d like to continue our discussion of the advances in certain aspects of pediatrics over the last 40 years. Several experts in the field are here to discuss and debate these topics. ~ S.S.

Stanford T. Shulman, MD, pediatric infectious disease physician: The topic is Haemophilus influenzae type b (Hib) disease and the development of Hib vaccine. Dr. Ram Yogev is going to lead the discussion.

Ram Yogev, MD, pediatric infectious disease physician: When Stan asked me to lead this discussion, I jokingly asked, “What is Hib again?” That’s because the vaccine has been such a success. Am I the only one already forgetting what Hib means? So I went online and checked how many publications there were on Haemophilus influenzae infection 40 years ago. I found that in the last 40 years, Hib was mentioned in close to 9,000 publications, yet in the last 4 years, there were only 800 mentions. I think by itself, that tells us the effect of this specific vaccine on our lives.

In 1975-1976, when I was a young attending, I was shocked to find out that some patients with Haemophilus influenzae meningitis were sent home on oral chloramphenicol. So before I treated my first patient, I decided to canvas 20 families. I called to find out if their child was still alive, especially since at the time there was some literature written by famous clinicians, such as Ralph Feigin, that suggested that chloramphenicol may work well. When I called, I found that all the patients were doing well. So I decided to evaluate the pharmacokinetics for oral versus IV chloramphenicol, but my paper was rejected from two really famous journals, with one reviewer — a famous infectious disease person — saying, “Dr. Yogev should consult with a better infectious disease person who understands that no medication can give a higher blood level after oral rather than IV administration.” During this whole saga, I was able to follow the development of pharmacokinetics in pediatrics, which is a fascinating field. Regarding chloramphenicol, both the IV and the oral forms are hydrolyzed in the liver. Because we gave the IV drug as a push, because the child had been very sick, it was found later that almost 70% of the chloramphenicol succinate given intravenously was in the urine. So the end result was that most of the oral chloramphenicol was able to work. The Europeans knew this, and so they were treating patients orally while we were still struggling.

But the real change that would be impressive to people of my age plus or minus 10 years, was due to the Hib vaccine. Back then, there was a published report of one hospital with 6,200 kids with meningitis. There were also large numbers of cases with epiglottitis and pneumonia and sepsis. But the Hib vaccine, developed and implemented in the late ’80s/early ’90s, really made a major difference, to the point that in countries where more than 80% of their pediatric population receive the vaccine, Hib has practically disappeared.

Also anecdotally, about 2 years ago, I was called in the middle of the night by a resident who could not understand why our microbiology lab was not good. It told him that the patient had a bacterium called Haemophilus influenzae in the CSF. He said he couldn’t believe it, because it is now so rare in the US, Europe, and the like. But with the development of the Hib vaccine, we were afraid we were going to see a shift in bacteria. If you look at how many Hib meningitis cases there were 40 years ago, compared with non-typeable or type a, the type b reigned and the others were almost unheard of. Now it’s the other way around — the other types are relatively much more common, and Hib is almost unheard of.

Hib is much reduced now in the developed world, but in 2006, the World Health Organization (WHO) suggested that there are still close to 5 million children worldwide who still develop Hib disease yearly, and almost 350,000 of them die. Unfortunately, the most pressing issue is that if the vaccine costs more than $3 per dose, many countries will not make it mandatory.

With Hib and Streptococcus pneumoniae vaccines, we see more non-typeable Haemophilus influenzae causing otitis media and sinusitis, which is not widely appreciated. This is important because Haemophilus influenzae has a much higher percentage of resistance to amoxicillin compared with S. pneumoniae, and as all of you know, the AAP still recommends amoxicillin as the drug of choice for otitis media. We need to start questioning if this is the best treatment for otitis media, with the changes in bacteria we are seeing now in otitis media and sinusitis.
The Hib vaccine has had an effect on pneumonia with reduction of almost 20% of pediatric pneumonia caused by Hib. That is not far from what they’re seeing now with *S. pneumoniae* using the same definitions. So the reduction in pneumonia cases is also showing us the importance of Hib vaccination. Recently, we have accepted that influenza vaccine also has such an effect, and obviously there are other vaccines that have proved themselves.

However, several populations are still vulnerable to Hib disease despite vaccination. For example, Native American populations are up to six times more prone to get Hib infection. In the US, Alaskan natives and Navajo Indians are still getting Hib disease. Studies in Europe and the United States now question if the three primary injections and one boost at around 15 months of age are sufficient, or if we need to do something more to protect these populations, especially if the number or people around them who carry *Haemophilus influenzae* or other bacteria will not give them a boost in immunity.

Because the younger generation of physicians is not familiar with Hib, recognition of clear cut cases may be delayed, or an antibiotic may be given for the wrong bacteria. This might cause an increase in complications in some cases.

**Lance E. Rodewald, MD, Director, Immunization Services Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention: Haemophilus influenzae was the eighth disease to become preventable through routine vaccination; now that’s doubled to 16 vaccine-preventable diseases. So the Hib vaccine sort of ushered in a new era of vaccine development. One of the key technologies brought forward with this vaccine was conjugation, and now we have two other conjugate vaccines, of course: the pneumococcal conjugate and the meningococcal conjugate vaccines.

Since then, there also have been vaccines introduced against hepatitis B, hepatitis A, varicella, rotavirus, and human papillomavirus, and then influenza is recommended for routine vaccination for children. The Hib vaccine really showed the way to start taking more control of these vaccine-preventable diseases. One of the other populations still vulnerable to Hib disease are children whose parents have decided not to get them vaccinated. During the recent Hib shortage, there were five cases of invasive Hib disease in Minnesota children whose parents elected not to get them vaccinated, leaving them vulnerable, with at least one death. This disease has never been completely eliminated; it’s still out there waiting to find a child who has not been protected.

**Dr. Yogev:** There is now more effort to combine several vaccines into one injection because there are so many of them. Now we have new vaccines that have *Haemophilus influenzae* included.

A few years ago, there were published reports of an increase in *Haemophilus influenzae* cases when the Hib vaccine, I think in Netherlands and the United Kingdom, was given in combination with DTaP. There was a DTaP Hib combination in which there was an interaction between the pertussis component and Hib that caused the Hib to induce lower antibody levels. When a vaccine is approved, we need to make sure that the lower Hib antibody levels exceed 0.15 mcg/mL for long periods of time. We might see that some combination vaccines could cause some problems because they don’t achieve this requirement.

**Dr. Rodewald:** It’s really important to keep close track of that. That heightens the importance of good disease surveillance and serotyping. In the past 40 years, other vaccine milestones have occurred: polio was eliminated in the US in 1979; measles was eliminated in 2000 for indigenous transmission; and rubella for indigenous transmission in 2005. So *Haemophilus influenzae* is a great success story, adding to a powerful program that helps protect children from preventable diseases — a clinical preventive service that saves lives and dollars at the same time.

**Stan L. Block, MD, FAAP, general pediatrician:** It used to be that one in 200 kids got Hib disease of some sort. It was a pediatrician’s nightmare because it meant you had to do many spinal taps and blood cultures and do aspiration of cellulitis. Also, I have been in the OR intubating a baby with epiglottitis. So the Hib vaccine has had a huge effect on quality of life for the pediatrician. Add the new pneumococcal vaccines Prevnar 7 and now Prevnar 13 and you get a major change in the way we approach kids with fevers, blood cultures, CBCs, etc. So when you get phone calls at night from the parent of a child with a 104° fever, you rest assured asking, “Has the child had his/her vaccines?” and you know you are on pretty good ground to reassure the parents that their child is going to be OK until tomorrow if vaccinated.

Now with the meningococcal vaccines, we still need to wait for the addition of meningococcal group B (which is now undergoing clinical trials). This could mean we will eventually have a pentavalent meningococcal vaccine in the near future for the infant, child, and teenager, which is going to make life much more bearable and less fearsome when a febrile child or a child with petechiae comes into your office.

**Dr. Shulman:** We’ve had an extremely successful and informative discussion and I really want to thank everybody for their contributions in discussion and presentations.

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