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by John D. Nelson, M.D. and George H. McCracken, Jr., M.D.

vaccine as discussed in the February 1992 issue of the **Newsletter.**

THE PERILOUS PNEUMOCOCCUS We have great concern for the increasing prevalence of relatively or absolutely penicillin-resistant pneumococci coupled with the increased relative frequency of pneumococcal diseases as a result of universal *Haemophilus* vaccination. For example, we recently managed a 9 month old infant with pneumococcal meningitis who failed to respond adequately to ceftriaxone therapy. After 6 days of treatment he still had a positive CSF culture. He promptly responded to vancomycin therapy. The organism had the following minimum bactericidal concentrations (MBC), expressed in μg/ml:penicillin, 4; chloramphenicol, 8; ceftriaxone, 8; and vancomycin, 0.25. This case is similar to the case by Bradley and Connor published in our journal (**Pediatr Infect Dis J** 1991;10:871) and to a report by Sloas et al that will appear in the August issue. Additionally, we managed recently a 3 year old boy with pneumococcal endocarditis caused by a relatively penicillin resistant strain (MIC, 0.25 μg/ml). He responded satisfactorily to very high dose penicillin (500,000 units/kg daily) given intravenously for 6 weeks and the C-reactive protein and sedimentation rate returned to normal values. However, the serum bactericidal titer against the organism was only 1:8. Two weeks after stopping therapy the affected pulmonary valve was removed and the valve containing the vegetation appeared unremarkable to the surgeon. This was not the case histologically where acute inflammation and Gram positive cocci were observed. We need new agents that are active against these strains, especially when they cause infection of difficult to treat sites like the meninges or heart valves.

NPIDS SURVEY At our recent 1992 National Pediatric Infectious Disease Seminar in Washington, DC we again asked the almost 600 registrants to answer some questions regarding their prescribing habits. Of the 482 respondents the majority were pediatricians (75%), the remaining being infectious disease fellows (8%), residents (5%) family practitioners (4%) and pediatric nurse practitioners or physician assistants (4%). As to which antibiotic was their first line drug for acute otitis media, 91% said amoxicillin (87% in 1991). If that treatment fails, their usual backup drug for acute otitis media was Bactrim/Septra (29%), Augmentin (29%), Ceclor (22%) and Pediazole (17%). These results are similar to those last year except that Pediazole fell from 26% and Augmentin increased from 18%. For treatment of acute sinusitis, amoxicillin (58%) and Augmentin (26%) were the winners with Ceclor (8%) and Bactrim/Septra (6%) lagging behind.

We asked several questions regarding management of streptococcal pharyngitis. For diagnosis 45% of responders use the culture exclusively, 40% a rapid test with culture backup for a negative test, 8% a rapid test and culture for all and 7% the rapid test exclusively. The latter two options are inappropriate since a culture is not needed when the rapid test is positive (there are very few false positives) and the diagnosis will be missed too often if the rapid test is used exclusively (there can be from 10-35% false negative results). Regarding management of the child who has a clinical and bacteriological relapse of strep throat after penicillin therapy, 50% preferred a cephalosporin and 38% penicillin for retreatment. Rifampin and Bicillin or clindamycin was the choice of 6% each. We were surprised that 13% of responders routinely obtain a throat culture after a successful course of antibiotics for strep throat. (It is usually not avisable.)

For the choice of *Haemophilus influenzae* type b vaccine, 70% use HibTITER, 16% ProHIBit and 14% PedvaxHIB. Twenty-eight percent of physicians routinely start hepatitis B immunization in all newborns. We asked the registrants what they prescribed for acute bronchitis and were modestly surprised that 52% use an antibiotic whereas 48% administer symptomatic therapy.

25 Harrisville Road,
Tuakau,
New Zealand.

1 May 1993.

Ref No: 93.1406

Dear Mr Birch,

This is a follow-up letter regarding the Haemophilus vaccine, because the most recent issue of the Lancet has confirmed suspicions that while this vaccine may assist in eradicating Hib, the vaccine will essentially leave a microbial "hole" which appears to be being filled with other organisms.

This has happened in the past as detailed in a joint letter to the Infectious Diseases Journal amongst the enclosed documentation.

I believe that the subject of this letter could perhaps have more importance than my previous letter, because the real question that parents will want the answer to, is this:

Will this vaccine solve the problem of my children catching Haemophilus? In other words, will it work? The answer to this one is according to Heikki Peltola, No, not entirely, (See latest Lancet) because a vaccine cannot be given to prevent the non-capsular haemophilus type B, or the non-serotypable haemophilus strains, which appear to becoming more prevalent with the use of the Haemophilus B vaccine.

On top of that, parents may not think to ask another perhaps more important question:

Will Haemophilus be replaced with something which is:

a) just as bad, and
b) potentially untreatable?

Most parents would not know to ask that question, because it would not occur to them that this could happen.

The answer to this question could well be as follows:

Journal of Paediatric Infectious Disease: June 1992:

"The Perilous Pneumococcus. We have great concern for the increasing prevalence of relatively or absolutely penicillin-resistant pneumococci coupled with the increased relative frequency of pneumococcal diseases as a result of Universal Haemophilus vaccination."

"We need new agents that are active against these strains, especially when they cause infection of difficult to treat sites like the meninges or heart valves."

Journal of Paediatric Infectious Disease: October 1992:

"Drs Leggiadro and colleages show a substantial REDUCTION in cases of invasive Haemophilus disease admitted to LeBonheur Children's Hospital, Memphis from 1982 - 1991... Of concern was a two-fold increase in the rate of pneumococcal disease in 1991."

Lancet, 3rd April 1993 page 851: talking about Non-capsular Haemophilus influenzae not covered in the vaccines:

"Infections due to these H influenzae strains are, after the implementation of Hib vaccines, likely to persist and represent a substantial proportion of the serious infections cause by this species."

and talking about both non capsulated and non serotypable haempohilus, and other types of haemophilus they go on to say:

"Furthermore, the relative importance of such organisms may increase because of the general intoduction of type B polysaccharide vaccines, which will greatly diminish invasive Hib disease but not systemic infection caused by non serotypable strains or H influenzae of other capsular type."

"...the proportion of H inflenzae disease caused by these strains in the Oxford region would have increased from 6% to 36%."

And more definitively, in the same issue of Lancet, from Heikki Peltola in Finland, the country that the "Immunisation" Committee so likes quoting, comes this:

"So is the H influenzae problem being solved? Unfortunately no. The more the vaccines are used, the greater, proportionally, will be the role of the non-capsular H influenzae that are a major cause of acute otitis media, sinusitis, exacerbations of chronic bronchitis, and other mostly respiratory infections."

Furthermore, our unimmunised children probably already have immunity to haemophilus type B. If by introducing this vaccine in New Zealand, haemophilus is replaced by other, more untreatable types of meningitis, the medical profession will have unnecessarily increased the risk of both immunised AND unimmunised children catching these new diseases.

Since parents who do not immunise their children, do not want this vaccine, we deeply resent any change in circulating microbial flora being forced upon us by those who want to use this vaccine, because at present, the circulation of haemophilus type B keeps these other potentially more dangerous organisms in control.

This is how I would put the above medical situation in layman language. In shooting the white wolves (hib) to stop them eating the rabbits (babies), some black ones (other bugs) are moving in to fill the hole where the white ones (hib) left off.

This to me is an appalling solution, because the country would then CONTINUE to use this vaccine, (to the pharmaceutical company's profit) while creating the NEED to develop new drugs

and new vaccines (more profit for the pharmaceutical companies, and taxes from the people) to combat the problems created BY USING the Hib vaccine.

The only people pleased about this would surely be the companies that research these drugs and vaccines.

The use of this new vaccine may be seen as the ideal short term solution, but the long term cost to the country in Hib vaccine, treatment of the newer diseases etc would seem to me to be unacceptable in the light of the fact that if parents are taught what to look for, and if Hib is caught early, it is easily treatable - far more so than pneumococcus meningitis. Perhaps we need to be considering educative measures, rather than creating other more long-term problems.

4 = PREVNAR

The "replacement scenario" is exactly what happened in America when Adenovirus vaccines were introduced to control type 3, 4 and 7. It did that, but the void was filled with other adenovirus types which did all the same things as 3, 4 and 7. However, in that incident, the U.S.A. withdrew the vaccine (except for the military) to allow the 3,4 and 7 to come back and balance the situation.

The most important question to me is:

"Will the New Zealand Health Department stand back, look at the new developments and decide to use caution and postpone the introduction of this vaccine?"

While I would like to think that they are big enough, and brave enough to say, "Hang on, lets relook this..." I feel that it is unlikely, because too much has been said, and there is so much professional vested interest involved.

Should this long-term scenario develop in New Zealand, as it is overseas, it is my opinion that that responsibility lies with you, as Minister of Health, because overseas, it did not occur to the medical authorities that it would happen. By drawing your attention to these facts, you now KNOW that it IS happening. On the other hand, it could well be that your medical advisors will consider that this is, yet again, me misinterpretting medical literature! An easy escape!

I will be ensuring that these above facts are well circulated, because so often political decisions are made for short term expediency. Then the long term disastrous effects are left for someone else to clean up - usually at the tax-payer's expense. Are you as Minister of Health prepared to accept the responsibility for these implications?

On recept of your replies to this letter, and the last letter, I will make an appointment to see you in person.

Sincerely,

After a slightly more sedate consideration than last time, on 22 April 1993, the reply said:

"We are not inclined to publish your letter because to date there are no data from the United States and Finland that substantiate an increase in Haemophilus disease caused by non-type b strains after vaccination of the population...Incidentally, we were fascinated by your analogy with adenovirus infections after vaccination. Is there documentation of the change in adenovirus types after vaccination? We would very much appreciate receiving the reference for this."

Funny they weren't "fascinated" the first time...

Dr Morris educated them, and his final paragraph in his reply (21 October 1993) reads:

"Information in the above quoted passages and in the attached references provides a pathway to the fascinating adenovirus vaccine story. That this story is apparently unknown to the editors of PIDJ is the basis for another fascinating story."

In the meantime I had written to the then Minister of Health on 23 March, and 1 May 1993, detailing my concerns and asking key questions, one of which was:

> *"Will the incidence of other serious infections (black wolves) rise as a result of the demise of HIB (white wolves)?"*

In his reply on 3 June 1993, Mr Bill Birch advised me that his advisers had advised him that:

"The short answer is that this is unlikely. The papers that you included with your latest letter show that the relative importance of other forms of meningitis increase, but the INCIDENCE remains the same. The only incidence that changes is that of HIB meningitis. And this incidence falls by 90% of its pre-vaccination rate in both of your articles that show figures. So, other causes of meningitis have not filled the gap left by HIB. The white wolves have not been replaced by black wolves to use your analogy. ***There are just fewer cases of meningitis (wolves) overall****, and the reduction in cases is entirely due to a reduction in meningitis due to HIB (white wolves)."*

IF A VACCINE is being so useful and NOT affecting any other disease statistics EXCEPT reducing one, surely there should show a REDUCTION in the total number of disease admissions to hospital — NOT the increase noticed over the last few months? Evidently at that time the advisors to Bill Birch thought we were cruising just nicely.

Another article I came across in the Arch Ped Adol Med Journal Jan 1994, pg 49 discussed the pre-vaccine Haemophilus decline in all groups but being most dramatic in the unvaccinated under 18 month old group, this way:

> *"This is consistent with findings from other reports, and it suggests that immunisation is not responsible for all of the falling incidence of Hib disease."*

Refs: JAMA 1993;269:221–226/JAMA 1993;269:227–231/JAMA 1993;269:246–248.

But let us not nit-pick. ALL articles said how wonderful the Hib vaccine was. It has been hailed as one of the safest, state-of-the-art vaccines which is the bench-mark of medical ingenuity.

Let us be generous. Let us say that regardless of the incompleteness of the epidemiological data for America, that the recent claims of making the world a Hib-free planet using a vaccine might even have some basis.

BUT AT WHAT COST?

Hilary Butler

From: "Hilary Butler" <butler@watchdog.net.nz>
To: <mlipsitc@hsph.harvard.edu>
Sent: Wednesday, 12 April 2006 9:11 AM
Subject: An enquiry from New Zealand.

Dear Dr Lipsitch,

I've read all your papers on bacterial serotype replacement (or lack of) that I can find.

I find an anomaly which to me is very interesting. In every country that has used the Hib vaccine, including USA, Finland, Belgium, UK, and also New Zealand, though no-one here has publicised the fact, the use of the Hib vaccine was followed in all cases, with either medical articles , or newspaper articles (or both) which stated very plainly, that medical authorities were puzzled at the sudden increase in Pneumococcus infections. The first in your country was The Pediatric Infectious Diseases Newsletter, June 1992.

I drew to the attention of the then editor, John D Nelson, the importance of what had been said in relation to the fact that the same had occurred when USA tried to use adenovirus vaccines not just within military, but within civilian society as well. (It turned out he didn't know about that, so he was supplied with the information) At the same time was an item in the Pediatric Infetious Disease Journal, Volume 11, no 8 August 1992 page 661, which not only stated that there was a sharp decline in the cases which began in 1987, well before the use of the vaccine, so perhaps the possibility is that pneumococcus was already taking over.

The next item of interest was the Lancet, Volume 341, April 3, 1993 page 851which most definitely talks about bacterial replacement as a result of Hib vaccine.

the Lancet, Volume 345, March 11 1995 page 661 containes quite an impressive graph showing clearly that as Hib went down, pneumococcus increased. I'm not sure what else this can mean, except species replacement as a result of the use of the Hib vaccine.

Then the Lancet Volume 349, March 8, 1997, page 699 in an item called "increase in pneumococcal bacteraemia in Sweden" indicates the same.

Eur J Pediatr 1997 156 288 - 291 states "the introduction of large scale systematic vaccination against H. Influenzae type b has drastically changed the incide of BM in areas where it has been performed."

A recent article in plospathogens, September 2005, volume 1, Issue one called "The Role of Innate Immune Responses in the outcome of interspecies competition for colonization of mucosal surfaces" is an interesting and relevant contribution.

I notice Martin Malden in the Lancet is now also expressing concerns at the Men C vaccination campaign in the UK could create similar issues.

In New Zealand, I've watched as the use of a Menomune A vaccine in 1987, supposedly displaced MB A, to lead to an increase in Hib. However, at the same time, we saw an increase in Meningitis B here (which turned out to be a type unique to New Zealand, home grown, from the very area that had the Meningitis A vaccine campaign..). During the time

the Meningitis B was rising, the Health Department put the Hib vaccine in the schedule, and as everywhere else, doctors said they saw no more cases. But within 18 months the papers were full of an unexplained increase in Pneumococcal illnesses... However, homegrown Meningitis B became the prevalent bacterial commensal, and by 2000 was the leading cause of MB cases and deaths (about 75%). 2000 was the tip of the mountain, and by the time the MeNZB campaign started in 2004, levels were half way back down to other side of the mountain graph. Meantime, the increase in pneumococcal disease has increased again, to the point where New Zealand apparently has five times the rate of other developed countries, and no-one can work out why, though Dr Cameron Grant from Auckland is trying to figure it out.

We know in the veterinary world, that if you use antibiotics in chickens to eliminate some bacterial pathogens, other more serious ones walk right in to fill the space. I believe that is also part of the story, but the vaccines are the bigger part of the story.

It can't escape anyone when lining up the medical literature, that the use of Hib vaccine created the Pneumococcal increase, though you don't subscribe to that fact.

It also seems that the original work of Robert Good on meningitis, which he said in his book was never completed, has never been taken seriously.

That work showed that when you vaccinated animals (rabbits) against one specific type of meningitis, that they lost the ability to fight off all other types, which his laboratory had found they had, prior to vaccination.

The current dogma is that all these vaccines are safe and beneficial. I look around me at all these supposedly healthy MeNZB vaccinated children, and listen to the grapevine and hear that people who've never tried quackery in their lives, are lining up in droves to naturopaths and other alternative practitioners, because their children are not what they were before. Doctors and the health Department of course, say the vaccine is wonderful, and could not possibly be the cause.

A flashback here is interesting. In 1987 we did a Menomune A vaccination campaign here which went seriously wrong, and was whitewashed. There were serious reactions which were initially explained as hysteria. I've kept all the information, all the details, and the subsequent medical articles.

It's ironic to me, that many of the people seriously affected by the Menomune A vaccine, had identical symptoms to those I now read on the CDC website as being related to Menactra (though as usual, dismissed as the same as background levels, therefore by implication, irrelevant). In the children's cases here, in 1987, they were dismissed as hysteria, and when that didn't wash, paranoid parents were to blame, being hyped up by the errant media. I've kept all that information too.

That is all background information from someone who has for a quarter of a century sat here, and watched one disaster follow another and the relevant concerns dismissed as anecdotal and coincidental.

I don't think these issues either either coincidental, anecdotal or irrelevant.

So I have three questions for you, given that you are one of the few who has looked at serotype replacement issues.

1) If you line up all the graphs from all the countries... all the information that I've mentioned... and more...why, within 18 months of the reduction of Hib cases, did pneumococcus take its place as the primary pathogen in MOST countries after the use of Hib?

If the elimination of Hib wasn't the factor that created the hole into which Pneumococcus dropped.... ***what was*** the factor that led to an identical time frame in every country that used the vaccine?

Each country started it in a different year, but yet, the trend is the same.

2) This country is about to put Prevnar and possible Menactra into its vaccine schedule. Can you tell me, which MB will be the one to fill the gap that Prevnar, Menactra, Hib and MenZB potentially all create?

3) Have you gone back and studied ~~Robert Good's~~ original work with rabbits to work out why, on the administration of the first specific serotype vaccine, those rabbits then became more susceptible to other meningitis types?

Sincerely,

27/04/06 - corrected name = Lewis Thomas

Hilary Butler.