The Perilous Haemophilus or is it.....pneumonia

By Hilary Butler

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"CHILDREN SICKER AND LOTS MORE ATTENDING STARSHIP HOSPITAL"

So said the NZ Herald, 26 Dec 1995, A3. What has that to do with the title of this article?

There appears to me a coincidence which is rather remarkable, and I probably wouldn't have twigged to it, except that the NZ Herald, 15 April 1988, A2, had this heading: "COT DEATH INCREASE 'APPALLING'" which discussed the *"appalling"* increase in the number of cot deaths throughout Auckland in 1987, especially in July, the worst month on record. Shirley Tonkin was quoted as saying: *"We are just appalled by this increase, and we do not know why it is happening."*

The cot deaths increase occurred THREE MONTHS after the introduction of the nationwide blanket administration of the first Hepatitis B vaccine immediately after birth.

Interesting too, that a Department of Health memo dated 21 March 1988 circulated to all hospital and Area Health Boards, detailed that the first injection should be delayed until shortly before discharge home in the case of babies of healthy mothers because: *"Minor side effects from the first H-B-VAX injection in a newborn baby may be confused with more serious ill health."*

In 1988 the IAS and I were run off our feet with mothers who had distressed babies after this vaccine – and those were only from that 1–5% of the population who, according to the Health Department, knew about our existence. I heard from a nurse whose career was ruined by the hepatitis B vaccine, and from Public Health nurses who had had the vaccine and the following winter had had health problems never previously experienced.

Even more interesting was the fact that shortly after that memo, it was considered that the first shot should be given at six weeks.

The telephone line between Dr Ralph Edwards (then the Adverse Reactions doctor in Dunedin) and I was hot for 18 months about complaints from the toddler catch-up campaign and newborn babies. It's all fact – and mentioned inside one of the fancy reports filed in obscurity somewhere in the Health Department.

What has that to do with the first heading about 'Children sicker' in Auckland?

There is a saying that those who don't heed history are destined to repeat past mistakes.…

When the 26/12/95 NZ Herald article appeared, I read the fine print to find that from the beginning of July 1994 to the end of October 1995, there was a 23% increase in youngsters being brought into hospital and a 15% increase in admissions. This occurred just over one year after the introduction of TETRAMUNE in this country and two years after the introduction of ProHIBit (Hib vaccine for 18 month children and older), and in the year when the Health Department had flooded the media with reports of how the cases of Hib had fallen to rock bottom. We were told that this vaccine would ease the total work load of the paediatric staff but here we see more, sicker children than ever before.

BUT, I hear you say, there is no direct time connection with the Hib vaccine as was alleged with Hepatitis B. Read on! In the latest article: *"Doctors are noticing that the proportion of very young children admitted is getting higher and that generally, children seem to be sicker when they arrive."*

Interestingly they mentioned an increase in cases of pneumonia, asthma, meningococcal disease, fevers and bronchiolitis….that the reasons weren't clear, but *"lack of money to pay doctor's bills could be a factor."* That was the same reason they used in 1988 to explain the increase in cot death. The article went on to state that two Starship paediatricians are, meanwhile, probing the pneumonia increases.

What is the evidence linking pneumonia in the NZ Herald article heading with the Haemophilus vaccine?

One of the most direct (yet dismissed) pieces of research is in Paediatric Infectious Diseases Journal, December 1993, Vol. 12, 981 – 5, where there was an article looking at the safety of the Haemophilus vaccine in Kaiser, USA, from 1 November 1990, to 26 July 1991. The initial analysis of babies given TETRAMUNE (the one in use in New Zealand) showed that these children appeared to have a higher rate of hospitalisation for pneumonia than children who were given Hib and DPT in separate shots. (It's a shame there wasn't a third more valid control – children who had received no vaccines at all.) The article commented:

"This initial association was believed most probably to be a result of chance alone. The [Tetramune] vaccine offers the convenience of a single combined vaccine... " (p. 981).

"In addition to having an effective vaccine it is also important to administer the vaccine in a way that encourages parental and physician acceptance and minimises trauma to the infants receiving the vaccine."

"... The additional injections are associated with additional administration costs at each visit. Parents may also be reluctant to subject their infants to multiple injections at the same time. This either generates unnecessary return visits or reduces compliance with recommended vaccination schedules." (pg. 982.)

So what did the trial authors do?

"In this study there was no significant difference for rates of medical adverse events as observed from emergency visits between the two vaccine groups. However, a statistically significant increased risk of pneumonia was seen after Tetramune. To investigate this possible association further analyses were undertaken...Because of the known overlap between the diagnoses of pneumonia and bronchiolitis in clinical practice in this age group, the charts of all children with these respiratory diagnoses were reviewed by a single observer who was blinded to the vaccine status of these children." – pg. 985.

This analysis showed no significant difference in the rates of pneumonia between the two groups. The article then said:

"It was concluded that...the single observed association in the automated data of pneumonia with receipt of Tetramune was most probably caused by misclassification of the diagnoses in the automated data set, or by chance alone. Tetramune would appear to offer the convenience of a single combined vaccine offering protection... "

The authors seemed very eager to talk about the logistical and financial advantages of TETRAMUNE, and I couldn't help wondering if this was a case of re-working the data to fit the desired outcome. What would have happened if another evaluation was done by a paediatrician opposed to the use of Hib?

I filed this article under my 'think' pile until the December 1995 NZ Herald article, when I went back to the pile to find out when Kaiser introduced TETRAMUNE. 1989 was the first year that TETRAMUNE, and other new Hib vaccines were approved for use in children under 18 months and, by the end of 1991, nearly 75% of children

under two years of age had received the Hib vaccine, some separately and some together because they weren't sure about it.

The time lapse between the introduction of Tetramune and the increase in pneumonia in Starship is the same as the time lapse had been in the Kaiser study (and in Finland).

Is this a coincidence?

TETRAMUNE *did* what they said it would. It seemed to knock out Hib. The Kaiser study (Arch Ped. Adol. Med. Jan 1994 pg. 54) did admit that the rates of Haemophilus had been falling in the two, four and six month age group, previously unvaccinated, for some time before its introduction...yet it was amongst this very group of babies that the study was done for the *safety* of TETRAMUNE – the same vaccine we use in New Zealand.

Bells started ringing in my head. Some years ago, the first Swedish study of the Japanese acellular pertussis (whooping cough) vaccine was abruptly stopped because a larger number of serious infections and deaths were occurring in the vaccinated group than the unvaccinated. The raw data repeatedly came up with PNEUMONIA and MENINGOCOCCAL MENINGITIS.

But acellular pertussis is a DIFFERENT vaccine. True. So

what's going on here? First, here is some easy history you should know, and some other "coincidental" pieces of the jigsaw that need to be placed...

<u>CRASH COURSE IN HAEMOPHILUS HISTORY.</u>

Have you ever wondered why the name Haemophilus INFLUENZAE? A bit contradictory for a bacteria, don't you think?

About 1888 Robert Pfeiffer isolated the organism from the sputum of patients with influenza and, for the next 30 years, the medical community assumed that Haemophilus caused the 'flu. It wasn't until the 1918 – 19 flu pandemic that it became accepted that Haemophilus was a part of the normal bacterial flora in the upper respiratory tract and not necessarily the cause of respiratory disease. (pg. 300, VACCINES (BOOK) Harcourt Brace Jovanovich, 1988). The name remains a testimony to the misconceptions of the past.

Another interesting historical question regarding Haemophilus is: "Can we tell who will become sick as a result of H. Influenzae infection?"

The answer to that is "yes and no":

"The reports of genetic marker associations with invasive Hib disease risk and responses to vaccines support the view that genetic factors may influence disease susceptibility."

Trouble is that the immunologists haven't figured out enough to be able to say "you, you and you" yet. We know that certain groups are more LIKELY to get it but that also applies to meningitis caused by other than Hib as well. People who have immune system problems are more likely to get bacterial meningitis but the groups that can actually be pinpointed are few and far between.

"Academic", say the researchers. Why waste more money when a vaccine is now here to solve all clinical ills?

In February 1993 IAS newsletter readers were alerted to a seeming connection between the use of the Haemophilus vaccine and an increase in Pneumococcal disease in an article entitled DREAMERS AND THEIR APPRENTICES. To recap the story until that time, this is what had happened:

The June 1992 issue of Newsletter from the Journal of Paediatric Infectious Disease (JPID) stated:

"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."

After considerable discussion, on 27 July 1992, Dr Morris and I sent a letter to JPID:

"RELATIONSHIP BETWEEN PREVALENCE OF PNEUMOCOCCAL MENINGITIS AND UNIVERSAL HAEMOPHILUS INFLUENZA VACCINATION"

To the Editors:

In the Paediatric Infectious Disease Journal newsletter (1992;18:6) concern was expressed "...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 nine month old infant with pneumococcal meningitis who failed to respond adequately to ceftriaxone therapy."

These sentences could be taken to mean that concern was prompted by an increase in prevalence of diseases including meningitis due to infection with penicillin-resistant pneumococci and that the increase resulted from universal Haemophilus vaccination. How or why one circumstance resulted in the other is not given in the quoted sentences nor given elsewhere in the newsletter note. That prior administration of Haemophilus vaccine might increase on rare occasions susceptibility to pneumococcus infection was not entertained.

The sentences might also mean that universal Haemophilus vaccination resulted in a decrease in Haemophilus diseases including meningitis and that the void was filled by an increase in pneumococcal diseases caused by antibiotic resistant pneumococci. If this is the explanation, then solution of one problem has given rise to another and this new problem is difficult to treat with available antibiotics which gives rise to a new need: antibiotics that are active against pneumococcal strains that invade difficult to treat sites like the meninges and heart valves.

This apparent one step forward-one step backward situation is reminiscent of similar problems that accompanied early use in the 1960's of inactivated adenovirus vaccines to prevent respiratory diseases caused by adenovirus types 3, 4 and 7. The vaccines were highly effective in preventing disease caused by these types, but not effective in preventing respiratory diseases caused by the other 40 or more adenoviruses that moved in to replace types 3, 4 and 7. Soon after this situation was recognised, use of adenovirus vaccines, except for use in military personnel, was abandoned. It might be well when assessing the overall value of the current program of universal Haemophilus vaccination, to keep in mind the earlier adenovirus vaccine experience.

J. Anthony Morris, Ph.D. Bell of Atri, Inc.

Hilary Butler IAS."

On 29th July (quick response!) the reply came back, which said:

"We will have an item of clarification in the September Newsletter concerning the potentially confusing statement in The Perilous Pneumococcus item."

Before the "clarification" came another item came up – one which was already in press at the time of the above correspondence:

August 1992 JPID:

Kaiser study 130,000 children. "Only six vaccinated children developed invasive Haemophilus disease, five of whom had received only one dose. In a Letter to the Editors in the October issue, Leggiadro and colleagues will show a substantial reduction in cases of invasive Haemophilus disease admitted to LeBonheur Children's Hospital, Memphis, TN from 1982 – 1991. OF CONCERN WAS A TWOFOLD INCREASE IN THE RATE OF PNEUMOCOCCAL DISEASE IN 1991." (emphasis mine)

Note the year – 1991, which was in the 12 – 24 month period after the introduction of this vaccine. Just like in Auckland.

Then came the 'clarification'.

September 1992: JPID: *"A CHOICE OF WORDS: Dr J. Anthony Morris asked what we meant by "increased relative frequency of Pneumococcal disease as a result of Haemophilus vaccination that appeared in our item THE PERILOUS PNEUMOCOCCUS in the June 1992 newsletter; our statement reflects the dramatic decline in the number of cases of invasive Haemophilus disease we and many others have experienced in the last 12 months or longer as a result of vaccination. We did not mean to imply that the absolute number of cases of pneumococcal disease would increase: rather, the frequency relative to Haemophilus disease would become greater as fewer cases of the latter are encountered."*

On 10 April, after some interesting medical articles, Dr Morris fired off another letter reminding Dr Nelson of our previous letter, including a copy of it, and adding:

"Knowledge of past events is of value if it is of use in predicting future events. Thus in the 3 April issue of LANCET is a paper "population-based study of Non-typable Haemophilus Influenzae Invasive Disease in children and Neonates". It reports "Infections due to (non-capsulated) H influenzae strains are, after the implementation of Hib vaccines, likely to persist and represent a substantial proportion of the serious infections caused by this species... Furthermore, the relative importance of such organisms may increase because of the general introduction of type b polysaccharide vaccines, which will greatly diminish invasive Hib disease, but not systemic infection caused by NST of H influenzae of other capsular types.

"The episode in the 1990's with Hib vaccine is reminiscent of the experience in the 1960's with adenovirus vaccine. This is more so now than in July 1992.

"In light of the new information you might now think that messages in the July 1992 letter will be instructive for your readers. If so, permission for publication is granted."

J.A. Morris

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?

Is the medical profession assuming that the present increase in pneumonia is just part of swings and roundabouts of disease increase and decrease?

I thought it could be – until I read an article in *The Lancet*, 11 March 1995, Volume 345, p661, from Finland, the first country to use the Hib vaccine in a widespread fashion.

"INCREASE IN BACTERAEMIC PNEUMOCOCCAL INFECTIONS IN CHILDREN".

TEXT EXTRACTS:

"For comparison, the figure shows the declining occurrence of bacteraemic Haemophilus influenzae type B (Hib) infections in the coverage area of the hospital. Hib vaccinations started in Finland in 1986, and the last case of invasive disease in our hospital was seen in 1991. Thus our results suggest that following the disappearance of invasive Hib disease in children bacteraemic pneumococcal infections have increased. A similar, although less striking increase has been reported in Philadelphia."

"It is tempting to speculate that the increase in invasive pneumococcal infections is causally related to the disappearance of Hib disease. It is known that Hib vaccinations have reduced the carriage of H influenzae and pneumococci may have found a new niche in colonising children. Even though the reason for the increase in bacteraemic pneumococcal infections remains unknown, the increase is a clinical reality...an increase in systemic pneumococcal infections emphasise the need for effective pneumococcal vaccines for young children."

Now we have a clear link between similar patterns in Kaiser, Philadelphia, Finland and New Zealand. New Zealand statistics show that there has been a gradual increase in pneumococcus ISOLATES (isolates = presence on swabs of pneumococcus – not necessarily disease) since 1990, as there have been with several other nasties. Whether that is because they are LOOKING for it more now than before, or whether that reflects a real increase in disease, is not stated. There had been no media releases reflecting concern about any overall increase in the incidence of CLINICAL PNEUMOCOCCAL DISEASE (as opposed to isolates), which predominantly affects the elderly whose immune systems are weaker. The warning on 26 December 1995 only mentioned babies and young children.

Why is the difference between ISOLATES and DISEASE important?

The medical literature makes it quite clear, with studies done on healthy people showing that:

"Other organisms will be found in throat swabs. In general these have no relevance to clinical illness, and the laboratory should not report other organisms, including staphylococcus aureus, Haemophilus influenzae, and the meningococcus." (NEW ETHICALS JUNE 1994.)

An even better study in Acta Paediatr 1995; 84:566-4 found that when tracheal and laryngeal aspiration were performed on healthy children it was found the majority carry potentially pathogenic bacteria, and: *"we conclude that aspirates from the larynx and the trachea are of limited value in the diagnosis of bacterial PNEUMONIA in children."*

This would indicate that the carriage and exposure rate of bacterial pneumonia in children is as high as ever. The next logical questions are:

What has happened to make children, instead of just carrying the bacteria, actually come down with the disease?

<u>Two things:</u>

1. Indiscriminate use of paracetemol (See volume 8, No. 3 pgs 3, 4 and 5)
2. On the basis of the above it is my personal opinion that the introduction of the vaccine TETRAMUNE is the prime suspect for the increased number of sick children, either by suppressing the immune system allowing carriage of pneumococcal bacteria to become clinical disease, or by providing a new niche for the bacteria to increase its loading dose in children, resulting in clinical disease. Either way, the result is undesirable.

IS THERE TALK OF A CHILDREN'S VACCINE FOR THIS DREADED NEW THREAT?

ASM News, Vol. 60, No. 1, 1994 sounds concerned because the increase in the number of antibiotic resistant pneumococcal cases is pressing companies for vaccines. There are multivalent vaccines for adults (with very variable effectiveness rates!!!) but a current 23-valent vaccine offers no protection to children less than two years. Merck now has a conjugate vaccine being tested to see if they can prevent otitis media (earache) in children, but the reality is that it is projected to be at least year 2000 before any vaccine is available.

Which brings us back to where we started – the Herald article talking about sicker kids and more of them, and an increase in pneumonia. The first warning signs elsewhere in the world were there to see for those who chose to read – BEFORE they chose to introduce this vaccine to New Zealand.

If the Finland scenario of increasing pneumococcal infections continues here, and invasive pneumococcus disease (or even perhaps other new-niche-seekers) skyrockets in this country, not only will vaccinated children be at risk from pneumococcus, so will unvaccinated children **and** their parents.

WHY?

Older people who have not had the vaccine are usually immune to Haemophilus (and hopefully pneumococcus) anyway. They developed immunity prior to the age of five in most cases, and most likely our unvaccinated older children have done the same.

If, by using the Hib vaccine, the result is that everyone has to face a new threat in the form of greater carriage of pneumococcal bacteria in vaccinated children then what the medical profession has done, as I stated in my letter to Mr Birch, is SHOOT THE WHITE WOLVES (Hib) and replace them WITH BLACK WOLVES. Pneumococcus is a far more serious disease, and far more untreatable, with more antibiotic resistance than Hib ever had, and the vaccinated majority would be responsible for passing this on to both the unvaccinated minority and the older community. In other words, this vaccine changes the whole existing bacterial balance, and it could be THIS change that has led to more severe sickness overall.

It is, as Dr Morris maintains, repeating the Adenovirus vaccine scenario all over again. Except that the Adenovirus vaccine was removed from use in children and the previous balance in viral types was allowed to re-establish itself.

If the above scenario is true then we, as parents of unvaccinated children, could have every reason to resent the introduction of Hib vaccines. Especially if the solution put forward by medical people is likely to be a pneumococcal vaccine sometime in the future, in addition to the Tetramune.

And if the introduction of a pneumococcal vaccine leads to an increase in something else, what then?

Maybe its time to talk again to Dr John D. Nelson, Editor of *THE PEDIATRIC INFECTIOUS DISEASE JOURNAL*...I'm sure he will be as enthusiastic as ever to hear from us.

POSTSCRIPT

This article was delayed to see if other countries might voice concerns. The silence has been resounding, which leads to three possible conclusions:

1. Silence is golden

2. It is no longer an issue to them

3. Since there is a pneumococcal vaccine on the horizon, the benefits of the Hib vaccine still outweigh any risks.

I also wonder, on the New Zealand scene whether they even realise or accept the reality of vaccines changing bacterial flora in a community.

[Vaccination] [Hilary Butler]