Acellular pertussis---

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The traditional pertussis vaccine has been a great cause of concern all through it's existence because of the persistent occurrence of serious side-effects. Hundreds of brain-injured children never stopped either the vaccine manufacturers or the health authorities from continuing the production and the use of the whole-cell vaccine. But they did see the need to search for a new, less aggressive vaccine quite a while ago.

The idea was to isolate the antigens needed to elicit an efficient antibody response with the exclusion of those responsible for the major reactions to the vaccine, such as inflammation of the brain. It took many years before any such vaccine was considered ready for production and large scale use. Japan started using an acellular vaccine in the autumn of 1981. The USA licensed the first acellular pertussis vaccine for use in infants and children two months of age and older for the primary series of immunisations in July 1996. Connaught Laboratories launched its 'TRIPEDIA' in 1992 as a fourth and fifth booster dose, and in 1996 for the first three doses; Lederle marketed 'ACELIMUNE' for fourth and fifth doses in 1991, and for the first 3 doses in 1996.

EFFICACY

It is hard to prove the efficacy of a vaccine if no agreement exists upon something as basic as a definition of the disease, and if no one knows what is a protective antibody level. Yet, these problems do exist. A 1996 article highlighted upon exactly these issues. "No serologic correlates of immunity have been identified", the authors state (12).

In 1984, the Japanese published the results of a trial with an acellular vaccine with two haemagglutinins on 5000 children (1).

Mark Kane, MD, of the World Health Organisation, said in August 1996 that the new vaccine had no significant advantage in efficacy over the old vaccine (3). A study in Senegal (7) even revealed inferior results compared to the whole-cell vaccine. "Beginning 28 days after the third vaccine dose, the overall ratio of pertussis incidence in the DTaP group relative to the DTwP group (RRac/wc) was 1.54(95% Cl' 1.23-1.93)" (7).

"Serum antibody concentrations before boosting *(at 15 to 20 months of age)* were lower than those obtained I month after the primary immunisation *(i.e. at* 7 appear to *months)"* (6). As antibodies drop significantly between 7 and 17 months, why are we so confident that immunity lasts long enough to protect throughout life? Or is the next generation of articles going to insist on booster shots every 5 to 10 years?

Miller and Escola, in a controversy on acellular pertussis vaccine, write in 1998: "We agree that there are still, many questions remaining about the use of acellular vaccines, such as the need for boosting and whether they will protect to curtail circulation." (8).Yet, production and general use of the vaccine started quite a while ago.

In general, five-component vaccines are considered to be more effective than two or three-component vaccines, as to their capacity to elicit antibodies. Yet, there is still conflict of data, as some sources claim equal efficacy for monocomponent vaccines (10). Poland (8) concludes from a study by Olin et al in Sweden (9) that there was no significant difference in efficacy between a whole-cell vaccine and three acellular vaccines, against more severe pertussis.

SAFETY

The data on the safety of the new acellular vaccine are contradictory. The Japanese study (I) e.g. mentions that "the vaccine does not have detectable side-effects", whereas the introduction of the same article says that "it is less than one-tenth as toxic as whole-cell vaccine...". How can a quantitative comparison be made if there is "no detectable side-effect" at all? Poland (8) argues that in a recent Swedish vaccine trial, there was no benefit of the acellular vaccine over the whole-cell vaccine as to efficacy nor as to "the frequency of serious adverse events, including hypotonic hyporesponsive episodes".

Local side-effects are generally admitted. They consist of redness and swelling.

Systemic reactions. however, also occur. Examples are fever, drowsiness, irritability, prolonged, high-pitched crying and seizures.

In one study (4) there was no difference with the old vaccine with respect to fussiness, antipyretic use, drowsiness, or anorexia.

Uberall noticed convulsions within three days of vaccination occurred in 1/15,912 doses in DTaP recipients (5).

Persistent inconsolable crying, a sure sign of brain inflammation, was present in 1/497 doses (5).

High fever (<40.5°C) was observed in 1/16,239 doses (5). One hypotonic-hyporesponsive episode was observed in 4,273 DTaP recipients (5).

Fever, injection site redness, swelling, and pain increased in prevalence with increasing numbers of injections (6). "For children receiving DTaP as a fourth dose, injection site redness and swelling occurred more frequently in DtaP primed than in DTwP-primed children" (6).

ADDITIVES

The preparation and conservation of the new pertussis vaccine imposes the use of certain substances which consequently can be traced in small amounts in the vaccine.

Ammonium sulphate was used in the Japanese vaccine.

Formalin is another additive used for the preparation (0.01%). The toxicity of this product is well known. It is used for the detoxification of the product, i.e. to reduce the induction of leucocytosis and of histamine sensitisation.

Aluminium hydroxide was used as an adjuvant (0.2 mg/ml) to enhance the production of antibodies.

Merthiolate is another toxic product added, discussed in an earlier article in this publication.

RESEARCH

It is a pretty bad habit of vaccine researchers to give several vaccines simultaneously where the effect of only one of them has to be studied and evaluated. Obviously this leads to confounding results.

In the early Japanese study e.g. diphtheria and tetanus toxoids were mixed with the pertussis component to be studied (1).

Like many studies, the follow-up time after vaccination for evaluation of side-effects in most studies was restricted to 48 to 72 hours. Needless to say that many serious adverse effects show up long after that time span; by definition they could never be mentioned in those studies. Nevertheless most of these studies pretend to prove the safety of the vaccine.

DISCUSSION

It appears that the acellular vaccine is less toxic than it's whole-cell predecessor. Besides, it would be difficult to produce a vaccine as toxic as the whole-cell pertussis vaccine. Whether this is good enough a reason to advocate it's large scale use still is a matter of discussion. The NVIC asked for the substitution of the old vaccine by the new one.

Apart from the better scores as to adverse effects compared to the old vaccine, the acellular pertussis also has a number of disadvantages. As Mark Kane, MD, from the WHO pointed out, the cost of the new one is higher and the production more complex, and the efficacy not better. He, therefore, questions the use of the vaccine for development countries. Apparently, in his view, a safer vaccine is important only for those who can afford it! As the article (3) ironically states: "...concerns over adverse events are unique to developed countries". "The DTP reactogenicity issue is not generally seen as a major problem in developing countries, It may be that parents and health providers are more tolerant of minor side-effects or there are fewer lawyers living in a less litigious society, but it has been our experience over many years in the EPI that the reactogenicity of DTP is not a major issue in these countries," Kane said. Of course there is no "issue" if you are simply lined up and physically forced to have your shot!

ADULT VACCINATION

Apparently, one of the important aspects of the acellular vaccine is the perspective of an adult booster vaccine.

The fact that whole-cell vaccines are considered to be unsafe for administration to adults and children over 7 years of age, whereas no one worries to give it routinely to infants, is strange enough.

Now, with the 'safer' acellular vaccine, the discussion is wide open to start pertussis booster vaccination programmes for adults, throughout life. Under the title 'FDA looking at feasibility of vaccinating adults against pertussis -- Protection wanes, and adults are becoming reservoirs of infection for children', an Infectious Disease News article on Internet opened the disussion last summer (July 1997). The apparent reason for concern is the observation that pertussis vaccination does not offer lasting immunity, whereas natural immunity is made impossible by childhood vaccination.

The result of this story is actually an <u>increase in pertussis in adults</u> during the past years. "Despite the availability of an effective childhood vaccine, pertussis cases have increased throughout the United States. Prior to widespread immunization programs

implemented in the 1940s, incidence of pertussis among those over 15 was only 3%; that number increased to 13.5% between. 1989 and 1991, according to a previous *JAMA* article" (11).

"The article in *JAMA* reported patients in the study visited a physician as often as nine times for cough symptoms, but none of the 153 patients was ever diagnosed with suspected pertussis nor was it included in the differential diagnosis. However, the prevalence rate for adult pertussis is 12.4%, according to the study."

On the other hand, the same article states that adult pertussis

is seldom severe, so it is unclear why adult vaccination is really necessary. The possibility exists that the expansion of the pertussis vaccination schedule will lead to more carriers and the increase of an infectious pool, thus further increasing the pertussis problem in an artificial way.

CONCLUSION

In spite of the euphoria in press and advertisements about acellular pertussis vaccines, a lot of questions and problems remain unanswered. To resume this with the words of G.A. Poland:

"Although many studies, costing millions of dollars, carried out in many countries, have been reported, we still do not understand true efficacy and reactogenicity differences between the available and candidate pertussis vaccines" (8).

From the literature studied we conclude that the currently available acellular pertussis vaccines

1. are not more effective in preventing serious pertussis;

2. are not more effective in preventing serious side-effects (although data are contradictory in this respect);

3. produce fewer local side-effects than whole-cell vaccines;

4. so far do not guarantee long-term immunity;

5. are much more expensive than the whole-cell vaccine;

6. contain the same toxic adjuvants as other vaccines.

We conclude that the new vaccines have a certain advantage over the old whole-cell vaccine, but not enough to suggest that they solved the problems that burdened the reputation of the old vaccine so badly. It is, therefore, not justified to call for mass vaccination on the basis of a presumed solution of the old disadvantages and the availability of a safe vaccine.

References:

1. Sato, Y.; Kimura, M.; Fukumi, H.; Development of a pertussis component vaccine in Japan. Lancet I, 1984; 8369:122-6

2. Aoyama, T.; e.a. Adverse reactions and an antibody response to acellular perlussis vaccine. J Pediatr, 1986; 109:925-30

3. Infectious Diseases in Children:Acellular pertussis vaccines may be impractical for developing countries. Infectious Diseases in Children, Internet Home page, August 1996.

4. Comparison of 13 acellular pertussis vaccines: adverse reactions. Decker MD; et al. Pediatrics, 1995; 96:557-66

5.Uberall MA; et al Severe adverse events in a comparative efficacy trial in Germany in infants receiving either the Lederle/Takeda acellular pertussis component DTP (DTaP) vaccine' the Lederle whole-cell component DIP (DIP) or DT vaccine. The Pertussis Vaccine Study Group. Dev Biol Stand, 1997; 89:83-9

6. Pichichero ME; et a!. A safety and immunogenicity comparison of 12 acellular pertussis vaccines and one whole-cell pertussis vaccine given as a fourth dose in 15-to 20-month-old children. Pediatrics, 1997; 100(5):772-88

7.Simondon F; et al. A randomized double-blind trial comparing a two-component acellular to a whole-cell pertussis vaccine in Senegal. Vaccine, 1977; *15(15):* 1606-12

8. Miller E et al. Issues about Pertussis vaccines. Lancet 1998 351:677-9

9.Olin, P.; et al Randomised controlled trial of two-component, three-component and five-component acellular pertussis vaccines compared with whole-cell pertussis vaccine. Lancet, 1997; 350:1569-77

10.Ad Hoc Group for the Study of Pertussis Vaccines. Placebo-controlled trial of two acellular pertussis vaccines in Sweden - protective efficacy and adverse effects. Lancet, 1988; i: 955-60

11.Nennin M, Shinefleld H, Edwards K.. Prevalence and incidence of adult peitussis in an urban population. JAMA, 1996; *275:1672-74.*

12. Unanswered questions continue to haunt pertussis vaccine research. AceUular pertussis vaccine trials showed safety and efficacy, but they did not address other questions. infectious Diseases in Children, July 1996.

[Vaccination] [Gaublomme] [DPT vaccines]