Whooping Cough Vaccine Research Revs Up

Scientific advances and increasing public fears about the vaccine are spurring researchers to improve the vaccine

At the heart of the current debate over whether the federal government should compensate children injured by vaccines is a battle over the safety of the whooping cough vaccine. Ever since inoculations against whooping cough became widely used four decades ago, researchers have acknowledged that the vaccine, though highly effective, often causes minor side effects, and, in relatively rare instances, causes severe reactions and even death. During the past several years, the vaccine has come under increasing fire by a small, vocal group of parents and some members of the media who have asserted that it is far more hazardous than the medical community is willing to admit and that researchers and vaccine manufacturers have dragged their feet and failed to produce a safer vaccine.

American Academy of Pediatrics

The whole cell vaccine

Acknowledged as "crude," the whole cell whooping cough vaccine has been the focus of persistent criticism for its side effects.

Scientific problems, as well as the vaccine's own superb effectiveness, have impeded efforts to develop a less toxic version. But many of these difficulties are gradually being overcome. New analytical techniques have helped researchers to better understand whooping cough itself, so that a considerable amount of research to develop a new, refined vaccine is presently under way. The pressure behind this research is a growing fear that criticisms of the whooping cough vaccine will seriously undermine public confidence in all mass immunization programs.

While recognizing that the vaccine does cause adverse reactions, public health officials have always emphasized that the benefits far outweigh the risk of side effects and the risk of contracting the disease. Whooping cough, characterized by coughing paroxysms that persist for several weeks, was once among the most deadly and infectious of all childhood diseases in the United States. In the 1940's, roughly 60 children per 100,000 died from whooping cough. But in the 1940's use of the vaccine sent the rate of death and incidence plummeting. On those occasions when inoculation campaigns have stopped, new epidemics occurred. In the late 1970's in the United Kingdom, for example, a major outbreak resulted when parents refused to bring in their children for whooping cough inoculations after widespread publicity that the vaccine was dangerous.

The whooping cough vaccine currently administered in the United States is essentially the same as the version introduced in the 1940's. While highly effective in preventing disease, it causes the most side effects among all the vaccines against childhood diseases. Minor reactions to the vaccine are common. Researchers at the University of California at Los Angeles reported 2 years ago that based on a study of 15,000 children, about 4 out of 10 experienced swelling, pain, and redness at the injection site. About the same proportion became fretful and developed fevers.

Severe reactions are much less frequent. Of the millions of children inoculated against whooping cough vaccine administered annually, 5 to 20 have died each year for the past 10 years following inoculation. Based on a population of 3.5 million children, the government estimates that about 50 children suffer permanent brain damage after vaccination. (Critics of the vaccine suggest it is linked with SIDS or Sudden Infant Death Syndrome, but scientists at the National Institutes of Health (NIH) found no causal relationship after conducting a case-control study. Centers for Disease Control (CDC) officials say these findings are buttressed by a similar but smaller study conducted in the United Kingdom. Precise rates of minor and severe reactions among the general population of children are difficult to pin down because often identical symptoms occur naturally in infants 1 year of age or less. Whooping cough vaccine is given in a series of five shots beginning at 2 months of age.

These minor and severe side effects are caused by what scientists readily acknowledge is a "crude vaccine." Because it is made from inactivated whole cells of *Bordetella pertussis*, the vaccine contains both toxins and antigens that induce an immune response. In contrast, vaccines against other diseases are typically produced from extracts of bacterial cells or viruses.

But the secrets of *B. pertussis* have eluded scientists because of several factors. According to an Institute of Medicine study,* scientists do not adequately understand how the disease develops or which components of the bacteria are toxic and which promote immunity. This is partly due to the fact that the organism is difficult to grow and that scientists lack a suitable animal model because *B. pertussis* only causes whooping cough in humans.

There was one vaccine, developed from extracts, that was widely considered an improvement of the whole cell version. After the whole cell vaccine was on the market for a few years in the late 1950's, some vaccine manufacturers began to test a vaccine formed from extracts of the bacteria. The new vaccine was basically made by washing whole cells in detergents, skimming off the liquid and purifying the product. Although a handful of companies tested such a vaccine, only one, Eli Lilly & Company, actually brought an extract vaccine to market. The Lilly vaccine, called Tri-Solgen, was sold between 1967 and 1972

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and, at one point, accounted for one-quarter of the whooping cough vaccine market. Then, in 1976, Lilly decided to get out of the biologics business altogether and ceased production of Tri-Solgen.

Wyeth subsequently licensed from Lilly the rights to use the name Tri-Solgen on its own extract vaccine and proposed that the Food and Drug Administration (FDA) immediately approve their product based on claims of similarity. FDA, however, told the company that the vaccines were not identical and that the company would have to perform more tests before approval. A government scientist said in a recent interview that the Wyeth version of Tri-Solgen, for example, was made from at least two different strains of *B. pertussis*.

According to a report by John B. Robbins, a scientist who formerly monitored pertussis vaccine development at FDA and now conducts pertussis research at the National Institute of Child Health and Human Development, Lilly's Tri-Solgen was associated with fewer minor side effects than the whole cell vaccine. There have been lingering questions about its true efficacy, however. Edward Mortimer of Case Western Reserve University and a pertussis researcher said in an interview that, in his opinion, Tri-Solgen was never properly tested for efficacy. "Some of us think it was not as potent as the whole vaccine," he said.

Mortimer and others also point out Tri-Solgen was never rigorously tested against the whole cell vaccine to compare their rate of severe side effects. Intuitively one might assume that a vaccine that causes fewer minor reactions would similarly produce fewer severe side effects. But with whooping cough vaccine, that is not necessarily so, says Philip Brunell, president of the American Academy of Pediatrics. For example, University of Texas researchers, led by M. Dianne Murphy, reported in 1983 that while some children who were inoculated with whooping cough vaccine developed systemic reactions, many of them did not develop local, minor reactions.†

All in all, the whole cell vaccine has been a tough act to follow. It successfully immunizes children 90 to 95 percent of the time and the severe side effects are relatively infrequent. Since Tri-Solgen was taken off the market, research on various extract vaccines has been conducted, but none of them has been found to be clearly superior in immunogenicity to the whole cell vaccine. The University of Texas study said that an extract vaccine did not induce as high an antibody titer as the whole cell version, although the difference was not statistically significant.

But research on extract vaccines has been stepped up in the United States and other countries. In the late 1970's, the development of better laboratory techniques to analyze cell proteins has allowed scientists to finally characterize the toxins and antigens of *B. pertussis*. Scientists have pinpointed a handful of components that are believed to play a critical role in inducing an immune response and are now trying to narrow down which ones are important. A government scientist says, "We're sculpting the molecule now."

In Japan, in fact, extract vaccines have been commonly available since 1981 because, like the United Kingdom, use of the whole cell vaccine dropped dramatically after public fears developed about the vaccine and a major outbreak of whooping cough followed, killing at least 40 children. Several Japanese companies were allowed to rush to market a number of extract vaccines formulated with different components. Six companies are currently licensed to produce extract vaccines.

Several experiments and clinical trials with a new vaccine are now under way or are about to begin here and abroad.

Key scientists in the United States and abroad, hoping to benefit from the Japanese work on extract vaccines, have been frustrated on several counts. The Japanese, they say, in their hurry to vaccinate, did not keep good records on what type of vaccine each child received. This makes it impossible for them to determine which, if any, of the various extract vaccines are effective. Some American researchers also report that the Japanese vaccines have shown high variability among lots and that some have not been well characterized. They note that the Japanese have not monitored children for severe side effects.

FDA and NIH tried to obtain some of the vaccines for clinical testing here but were unsuccessful until recently because Japanese manufacturers were concerned about potential liability, government scientists say. One of the Japanese extract vaccines has now been licensed by Wyeth and is being tested in small clinical trials under contract with the National Institute of Allergy and Infectious Diseases at Marshall University in West Virginia and at Vanderbilt University.

Several laboratory experiments and clinical trials with extract vaccines are currently under way or about to begin here and abroad at:

- Michigan Department of Public Health. Under another contract supported by the National Institute for Allergy and Infectious Diseases, the state health department is developing an experimental extract vaccine. Michigan currently produces for distribution within its borders whole cell whooping cough vaccine. David Klein, the institute scientist who oversees the $459,000 project, says that the study began in 1983 and will run for 3 years.
- The National Institute for Child Health and Human Development. A research team headed by John Robbins is developing an extract vaccine with one component. The intramural work on pertussis was funded at $415,000.
- Connaught, Lederle, and Wyeth. The three companies currently producing whole cell whooping cough vaccine are aggressively investigating extract vaccines, according to government scientists. Connaught and Wyeth last year cited liability problems and stopped distributing the vaccine. Now only Lederle sells the vaccine.
- China. Scientists there are gearing up to test an extract vaccine.

But even if an extract vaccine shows promise in small clinical trials, which are designed to examine safety, many scientists say that there is an ethical problem to be considered before larger trials to test for effectiveness can be conducted in the United States. Given the effectiveness of the U.S. domestic whole cell vaccine and the infrequency of adverse side effects, researchers question whether it would be fair to inoculate a large population of children with a new vaccine without knowing its efficacy.

In addition, Brunell said in an interview that to determine severe effects, a new whooping cough vaccine would have to be tested among "tens of thousands of kids" to compare it to the whole cell vaccine, and that kind of study would cost an enormous amount of money.

The ethical dilemma is being solved in part by Sweden, where a unique set of circumstances has set the stage for a large clinical trial on an extract vaccine. This fall, the Swedish government plans to begin a study that will test an extract vaccine manufactured by Biken, a Japanese research institute. About 2500 to

†"Evaluation of the pertussis components of diphtheria-tetanus-pertussis vaccine," *Pediatrics*, vol. 71 (No. 2), p. 200 (1983).

3000 children will be included in the trial, Marta Granstrom, a chief investigator in the study and an associate professor at the National Bacteriological Laboratory, said in a telephone interview from Stockholm.

The Swedish government, which manufactures vaccines for the country, used to produce whole cell whooping cough vaccine, but in the late 1970's it was revealed that its whooping cough vaccine had insufficient potency. Then, parents began to seriously doubt the safety of the Swedish whole cell vaccine. In 1979, the government stopped producing whole cell vaccine and, since then, Swedish children have gone unvaccinated against whooping cough. In 1982 and 1983, Sweden was confronted with the worst whooping cough epidemic in decades. Because the disease runs in cycles, the next epidemic is expected in 1986 and the Swedes are racing against the clock to inoculate children.

The Swedes are working closely with CDC scientists to design the trial and maximize the opportunity to collect data. Granstrom said that the research team would consider testing another extract vaccine if another one had been properly tested for safety.

American scientists speculate that a new extract vaccine might be on the market here within the next several years, if everything falls into place. An Institute of Medicine committee studying vaccine research reported in January that the public perception of adverse reactions to the whooping cough vaccine "is damaging generally to efforts to promote immunization and thus development of an improved vaccine merits special consideration."—**MARJORIE SUN**

This is the second of two articles on vaccines. The first article, which appeared in last week's issue, focused on vaccine compensation.

IOM's Future Under Review

Many members of the Institute of Medicine (IOM), the semiautonomous health policy branch of the National Academy of Sciences (NAS), were puzzled by a missive last month from IOM president Frederick C. Robbins. In a two-paragraph memorandum, Robbins informed them of the "extremely constructive" deliberations over a study of the institute's future and passed along an equally mystifying resolution by the Academy's council expressing support for IOM. The missive was puzzling because few of the institute's members were aware that IOM's future is in doubt, and even fewer had seen a copy of the study to which Robbins and the resolution referred.

Late last year, a committee chaired by Robert Sproull, former president of the University of Rochester, recommended major structural changes that would have integrated the IOM into the Academy's bureaucracy by eliminating its authority to conduct its own studies, would have brought it more under the control of the Academy hierarchy, and would have altered the criteria by which it selects its members. The review committee was established last summer by Academy president Frank Press to examine the structure and function of the IOM. According to Philip Smith, the Academy's executive officer, the review was just one of a series of studies of the Academy's operations that were begun when Press took over in 1981. The review was generally perceived within IOM, however, as a potential threat to the 14-year-old institute's autonomy.

It is no secret that relations between the IOM and the Academy have not always been harmonious. The institute elects its own members who are chosen in part for their willingness to participate in policy studies rather than for their professional eminence alone. In contrast, the Academies of Sciences and Engineering are elite organizations whose members are supposed to be elected solely on the basis of their professional reputations. The institute also has its own professional staff which is separate from the National Research Council, the operating arm of the Academies of Sciences and Engineering.

The Sproull committee, whose report still has been circulated only among the top echelon of the Academy and IOM, recommended that the IOM bureaucracy be brought into the National Research Council, a move that would bring the day-to-day management of the institute's studies more directly under the Academy's wing. It also recommended that the institute be renamed the National Academy of Medicine and that it develop new membership requirements. Academy members tend to look down on some IOM members whose prestige is in areas such as nursing, health economics, or law, rather than basic biomedical science. The possibility that the present membership be reduced drastically by attrition as their terms expire was raised speculatively. Finally, the Sproull committee recommended that IOM should undertake a broader range of health policy studies. In general, according to Robbins's interpretation, the report broadly supported IOM's basic mission and offered a mixture of criticism and praise of its performance.

The recommendations were reviewed by the IOM council in January and a detailed set of responses was forwarded to the council of the Academy. The IOM council rejected the notion that the institute be turned into a strictly honorific Academy of Medicine—a recommendation that was also firmly rejected by the Academy's council—and expressed concern that integration with the National Research Council would undermine IOM's identity.

At its meeting on 8 February, the Academy council decided to put off any decisions on implementing the Sproull report's recommendations until a new president of the IOM has been chosen to succeed Robbins, whose 5-year term of office ends in October. In essence, the council agreed that whoever is selected should have a role in deciding the future of the institute. The Academy has, however, decided to take control of the process of selecting Robbins's successor: the IOM's search committee, which was headed by Upjohn vice president Theodore Cooper, has been disbanded. A new nine member search committee has been named, with five persons chosen by Press and four by Robbins. NAS council member Paul A. Marks, who also belongs to the IOM, has been appointed chairman by the Academy. Cooper will be an IOM representative.

The Academy's resolution "doesn't say that any of the things (recommended by the Sproull committee) won't be done," notes Robbins. But any decisions should now involve the full participation of both institutions, he says. At the least, the members of both institutions may become aware that major changes are in the wind.—**COLIN NORMAN**