Editorial

Assessing benefit-risk ratios

Pertussis vaccine as a case in point

Helping individual patients and the general public to understand the benefits and risks associated with diagnostic, preventive, and therapeutic procedures is not easy. It is particularly difficult when the immediate benefits of the procedure are not evident, or when we ourselves are uncertain.

The problem is well exemplified by the recent public concern about the risks of pertussis vaccine, prompted by a National Broadcasting Company (NBC) documentary that, in the opinion of many in the medical community, grossly overestimated known risks from the vaccine and erroneously discounted its established benefits. Parts of this program were shown in Cleveland on the *Today Show* and other NBC programs. A combination of erroneous statements and vivid portrayal of children allegedly damaged by the vaccine unfortunately caused understandable consternation to many parents while outraging many members of the medical community. The initial response of many parents was to refuse pertussis vaccine for their children, but, happily, because of vigorous efforts by local medical societies, the American Academy of Pediatrics, the United States Public Health Service, the Food and Drug Administration, and individual physicians, the record appears to have been set straight.

This episode raises too many questions to discuss here, such as how much patients should be told and how best to do it, and the legal complexities of informed consent. Additionally, there are broader questions about the responsibility of the public media. Medically, an important question is how one assesses the benefit-risk ratio of vaccines, many of which do have some risk, as do other preventive, diagnostic, and therapeutic measures.

In addressing this question pertussis vaccine is an excellent case in point. The decline in morbidity and mortality from whooping cough in the United States and other developed countries has been attributed to widespread use of the vaccine since the 1940s. Vaccine efficacy in preventing whooping cough is established by well-controlled clinical trials.[1,2] But in recent years some have suggested that the nearly complete disappearance of mortality from pertussis is not due to the vaccine, but to other factors such as improved nutrition and better living conditions.[3] Cited as evidence is the decline in mortality from pertussis long before the vaccine was developed; infant mortality rates from pertussis, which were more than 4 per 1000 live-born infants in the first five years of this century, declined more than 80% by 1940, before widespread use of the vaccine.[4] Opponents of routine pertussis immunization argue that current low mortality from pertussis is therefore not due to the vaccine but to other factors that antedated the vaccine.

In addition to believing that the vaccine is presently superfluous, opponents condemn the vaccine because of its reactivity. Thus, they argue that the risks of the vaccine outweigh its benefits.[3] Those of us responsible for vaccine recommendations in the United States have also considered these questions and disagree.

In terms of risk, there is no doubt that DTP vaccine is more reactive than other childhood vaccines and that this reactivity is chiefly due to the pertussis component. Reactions to pertussis vaccine are of three types.[4] The first comprises local reactions, varying fever, and irritability for a day or two. The second includes certain systemic reactions of unknown importance, including a peculiar shock-like syndrome, persistent crying, excessive sleepiness and febrile convulsions. The shocklike episode occurs following about 0.06% of injections; persistent, unconsolable crying for more than an hour occurs in about 3.6% of individuals.[5] Febrile convulsions follow in approximately 0.06% of injections.

But the major concern is severe encephalopathy following pertussis vaccination, often associated with permanent brain damage and sometimes with death. First described 40 or more years ago, its frequency has been uncertain until recent years because of its rarity and confusion with other encephalopathic conditions in infancy. In 1967 a Swedish study indicated that about one in 170,000 children is so affected.[6] A more recent British study has suggested a higher figure—about one in 100,000.[7] Extrapolation of these data to the United States suggests that between 20 and 35 of the 3½ million children born each year incur disabling pertussis vaccine encephalopathy.

This is a risk that none of us likes, but it must be balanced with what would happen if widespread immunization with pertussis vaccine were abandoned in the United States. In brief, do the current benefits outweigh the risks? Would pertussis no longer be a serious public health problem, even without immunization, as suggested by vaccine opponents? All attempts to answer this question indicate that the vaccine prevents far more death and disability than it causes. In Britain and Japan where acceptance of pertussis vaccine declined markedly because of public concern about reactions, major epidemics of pertussis promptly occurred, particularly affecting young infants.[8] A similar recrudesence of pertussis with associated morbidity and mortality occurred in Sweden, where vaccine production was stopped because of technical problems in its manufacture. Further, pertussis

remains a major cause of childhood mortality in underdeveloped countries.[4] Finally, in the United States pertussis still occurs. I have seen several culture-proved cases this year.

Based on the Japanese and British experiences, between 35 and 60 deaths annually would result in the United States within two years if we discontinued pertussis immunization, and undoubtedly this number would increase in subsequent years as herd immunity declined. But projecting from the first 40 years of this century, including extrapolation of the decline in mortality prior to the vaccine, indicates that nearly 1000 deaths from pertussis would result annually without the vaccine;[4] in contrast, fewer than 10 now occur each year. Another analysis has indicated that mortality from pertussis would increase fourfold if routine immunization were to be discontinued.[9] It is important to point out that these studies consider only deaths; mortality from clinical pertussis is only the tip of the iceberg because larger numbers of children with pertussis, particularly infants, incur brain damage. Thus, in brief, we are talking about 20 to 35 children damaged, unhappily, by the vaccine in contrast to many more—perhaps several thousand—who would die or be damaged by the disease. Thus, although a precise number cannot be provided, we have no doubt about the highly positive benefit-risk ratio of routine pertussis immunization of infants and children. It is on this basis that scientific advisory groups continue to recommend routine immunization with the present vaccine.

The issue is further complicated by the fact that pertussis immunization, like rubella immunization, is a measure that protects others as much as, or more than, the recipient. The younger the child, the greater the mortality from pertussis will be. But by the optimum immunization schedule (DTP at 2, 4, 6, and 18 months and 5 to 6 years) infants are not adequately protected until approximately 7 months of age; thus, for the first few months the infants are dependent upon those with whom they come in contact, including siblings, being free of pertussis. Case-fatality rates and sequelae from whooping cough decline geometrically even in infancy, and by age of school entry are negligible. Accordingly, DTP "boosters" at 18 months and prior to school entry, as recommended, offer little direct benefit to the recipient child except for protection against a nuisance disease. But from the standpoint of younger siblings and other infants and the public health, we believe the benefit to be incalculable. For these reasons we continue to recommend five doses of pertussis vaccine as DTP: at 2, 4, 6, and 18 months and prior to school entry.

The problem with the vaccine is that until recent years the pertussis organism has been poorly understood in terms of its biologic and immunologic relationship to man. Indeed, it has not been clear which antigen or antigens represent the immunogenic moieties of the organism, which are responsible for the toxic phenomena of the disease or associated with the vaccine, or even whether they are the same. As a consequence, currently licensed pertussis vaccines are relatively crude, comprising whole killed organisms containing a multitude of antigens. But recent studies offer approaches to a "cleaner" vaccine. The organism appears to be better understood in terms of the protective and toxic antigens, and new techniques offer prospect of their separation and the production of a less toxic, fully immunogenic preparation.[10] But until such a

vaccine is available, I believe that the benefit-risk ratio of the current vaccine fully warrants its routine use.

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