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# The Pertussis Vaccine Controversy

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This article is based on the author's presentation at the Second Binational Symposium: United States-Israel, held in Bethesda, Md., October 17–19, 1983.

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**Synopsis**

*Over the past few years, there has been continuing controversy about whether the benefits of routine vaccination for pertussis outweigh the potential risks. Some of the epidemiologic and technical issues include ascertainment and reporting of cases, case definition and laboratory confirmation, identification and purification of antigens, vaccine potency measurement, vaccine efficacy, and vaccine safety. Other factors include legal and economic issues, ethical concerns, emotional overlays, and the role of the media. Much of the evidence for the benefits of pertussis vaccination arises from epidemiologic studies regarding the incidence of the disease and the effectiveness of the vaccine in preventing it. The very nature of epidemiologic data has contributed to the controversy, since there is virtually no epidemiologic study with absolutely incontrovertible results that allow only one interpretation. Nonetheless, available evidence indicates that the benefits of pertussis vaccination far outweigh the risks.*

OVER THE PAST FEW YEARS, there has been continuing controversy about whether the benefits of routine vaccination for pertussis outweigh the potential risks. The controversy involves not only the interface among epidemiology, politics, and policy, but also legal and economic issues, ethical concerns, emotional overlays, and the role of the media. In this paper I will first describe some of the epidemiologic and technical issues involved in the pertussis vaccine controversy and then discuss the impact these issues have had on the development and implementation of public policy.

## Epidemiologic and Technical Issues

**Ascertainment and reporting of cases.** It is widely felt that the diagnosis of pertussis is not considered in all circumstances where it might be appropriate and that there is substantial underreporting of cases in this country. One indication of the degree of undernotification is the fact that the number of pertussis hospitalizations in the United States reported through the National Hospital Discharge Survey exceeds the number of cases reported to the Centers for Disease Control through the routine

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Morbidity and Mortality Weekly Report mechanism. By contrast, data from the United Kingdom indicate that before that country's recent epidemic, only 10 percent of persons with diagnosed cases were hospitalized (*1*) and that during that epidemic, only 4 percent were hospitalized (*2*). As a consequence, reported morbidity data must be regarded as reflecting trends rather than representing an exact quantitative estimate of the occurrence of pertussis.

Problems in case ascertainment and notification contribute to debates about possible changes in the severity of the disease. Some claim that, with modern modes of therapy, pertussis has become a trivial illness, with essentially no serious complications or deaths (*3*). While it is clear that there has been a major reduction in pertussis mortality, the United States still has 5–20 deaths ascribed to pertussis each year, and a significant number of hospitalizations.

**Case definition and laboratory confirmation.** There is no widely accepted clinical case definition for pertussis, and laboratory confirmation is difficult. Bacteriological recovery of the organism is difficult, and the direct fluorescent antibody technique, which is often used for diagnosis, may not be reliable, particularly in laboratories where it is not routinely performed (*4*). Additionally, other organisms, particularly adenoviruses, may cause a whooping cough syndrome clinically indistinguishable from that caused by *Bordetella pertussis* (*5*). Finally, there is no readily available serologic test to confirm infection.

**Identification and purification of antigens.** There are many antigenic components of *B. pertussis,* and it is not yet certain which of these is necessary to induce immunity. As a result, it has not yet been possible to prepare more highly purified vaccines, and the current vaccine is a suspension of whole killed organisms, including components such as endotoxin. It seems probable that the filamentous hemagglutinating antigen (FHA) plays an important role in eliciting protection, but it also seems that the leukocytosis-promoting toxin (LPT), and possibly other components, may contribute to the induction of immunity (*6*).

**Potency measurement.** Potency testing for pertussis vaccines is carried out in a somewhat artificial setting: protection of mice against intracerebral challenge with pertussis organisms. This method of measuring potency has been shown to correlate with induction of clinical protection. However, since it is a bioassay, it is not as precise as direct measurement of antigenic mass or some other biochemical determination, and, since it involves intracerebral challenge, it may not be the optimal model to measure protection against a respiratory disease (*6*).

**Vaccine efficacy.** Typically, vaccine efficacy is measured in one of two ways. The first is by the ability of the vaccine to induce antibodies known to be protective. The second is by the ability of the vaccine to provide protection in the face of exposure. Although pertussis agglutinins can be measured in circulating blood, correlation of clinical protection with the presence and level of agglutinins is not as precise as one might wish. Although the presence of high levels of circulating agglutinins (1:320 or greater) is a reliable indicator of immunity, some persons with lower or unmeasurable titers of agglutinins may be protected on exposure to the disease. Measurement of the clinical efficacy of the vaccine in protecting those exposed is complicated by the difficulty of diagnosis and confirmation of infection.

Notwithstanding these problems, recent data on the clinical efficacy of pertussis vaccine indicate that the vaccine is protective in 70–90 percent of those vaccinated (*7*). It is also clear that the widespread use of pertussis vaccine in this country has played a major role in reducing the incidence of the disease (*8*). In the United Kingdom, pertussis vaccination levels have declined since 1974, and there have been two epidemics of pertussis. Disease incidence in various communities was inversely related to vaccination levels (*2*).

Problems in measuring vaccine efficacy also come to the fore when trials of new pertussis vaccines are considered: one cannot ethically carry out placebo-controlled trials, and, in the presence of vaccine, disease incidence is so low that very large study populations will be needed to demonstrate comparable or improved efficacy.

**Vaccine safety.** There has been considerable debate about the incidence of reactions, including more serious, potentially life threatening reactions, to pertussis vaccine. The major concern has been the possible role of the vaccine in causing acute encephalopathy with or without permanent brain damage, convulsions, and death (including death from sudden infant death syndrome).

Accurate identification of the role played by pertussis vaccine in inducing central nervous system (CNS) damage is complicated by the fact that there is no clinically distinct and recognizable "pertussis encephalopathy" and that pertussis vaccine is administered to infants at a time when CNS lesions due to other causes may become manifest. The fact that two events which are not uncommon in infancy—DTP (diphtheria-tetanus-pertussis) vaccination and first onset of convulsive disorder—may occur in close temporal relationship makes it very difficult to assess causality. There are many reports in the literature of central nervous system illness following pertussis immunization; virtually all have been characterized by "after the fact, therefore because of the fact" reasoning, without controls or consideration of background levels of incidence.

The most important controlled study of the occurrence of CNS damage and its relationship to pertussis immunization was the British National Childhood Encephalopathy Study, in which all hospital admissions due to CNS disease in infants between the ages of 2 months and 3 years were studied. The study was carried out from July 1976 through June 1979, and 1,000 cases (of a total of 1,180) have been reported (*9*). Two control children were selected for each case and matched for sex, age, and area of residence.

The study identified an increased risk of encephalopathy associated with receipt of pertussis vaccine. For acute encephalopathy, the frequency was estimated at one case for approximately every 110,000 doses of DTP; for encephalopathy with residual damage 1 year later, the estimate was one case for every 310,000 doses.

It seems unlikely that a study of this magnitude and careful design could ever be repeated or improved. Nonetheless, several criticisms have been aimed at the study, suggesting that the researchers might have overestimated or underestimated the relationship between pertussis vaccine and encephalopathy. The fact that other possible causes of CNS disease were not taken into account in the calculation might lead to a possible overestimate of danger associated with pertussis vaccine. By contrast, the fact that the study was limited to children admitted to hospitals—and therefore to relatively severe acute illness—might lead to underestimation of the rate of acute illness associated with pertussis vaccination (*10*).

The possible role of pertussis vaccine in precipitating sudden infant death syndrome (SIDS) was brought to the fore when four instances of sudden infant death, occurring within 24 hours of the infants' receipt of DTP vaccine, were reported from the State of Tennessee in 1979. A detailed investigation could neither confirm nor refute a possible relation between DTP vaccine and SIDS (*11*).

A more recently published study represented an uncontrolled retrospective assessment of infants who had died of SIDS. This study made the assumption that if there was no relationship between pertussis immunization and SIDS, there would be a random time relationship between receipt of DTP vaccine and SIDS. Since there was an increased frequency of history of receipt of DTP vaccine within the 24–72 hours prior to sudden infant death, the author proposed that there might be a possible relationship between the DTP vaccination and SIDS (*12*). However, it should be noted that (*a*) the study included only 30 percent of the SIDS deaths on which followup was attempted, (*b*) there was also an increased frequency of physician visitation in SIDS cases, and (*c*) the study relied on parental history of vaccination. It is quite likely that parents would tend to remember vaccinations that took place immediately preceding a child's death better than those occurring earlier.

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The most definitive study that has been conducted on SIDS is a multicenter case-control analysis of SIDS cases sponsored by the National Institute of Child Health and Human Development. In this study, each SIDS case in six catchment areas across the country was matched with two controls chosen for age, sex, and residence. Interviews were carried out with the parents of the SIDS infants and with the parents of the controls to ascertain a wide variety of factors possibly related to SIDS, including history of vaccination. Analysis of the first one-half of infants entered into the study (800 total) clearly demonstrated that fewer SIDS infants than healthy controls had received pertussis vaccine (*13*).

## Other Factors with Impact on Public Policy

Despite the epidemiologic and technical issues listed previously, the vast majority of U.S. scientists and public health officials believe that the benefits of pertussis vaccine far outweigh its risks (*14,15*). Nonetheless, there are substantial problems in converting scientific consensus into accepted public policy. These problems arise not only from the remaining uncertainties concerning pertussis and pertussis vaccine but also from a series of other factors impinging on the development and implementation of public policy.

*'The very nature of epidemiologic data has contributed to the controversy, since there is virtually no epidemiologic study with absolutely incontrovertible results that allow only one interpretation.'*

**Legal issues.** In this country, legal issues are important contributors to the controversy. Since, on occasion, pertussis vaccine may cause damage to the recipient, the question arises: What compensation shall there be for the injured recipient?

In at least six countries, there are mechanisms for providing compensation to those who are injured as a result of vaccination (*16*). In the United States, such a mechanism does not presently exist, although one has been advocated by a number of different groups (*17*). Consequently, an individual must sue in order to obtain compensation. Complicating this situation is the fact that, in 44 States, pertussis vaccination is required for first entry to school. Thus, the parents of a young child have little option but to ensure that the child is vaccinated, whether or not they themselves fully support the immunization process. If a vaccine injury occurs in the child, this may be viewed as an individual adverse outcome resulting from a societal mandate. Many persons claim that society should automatically provide support for those undertaking individual risk for societal benefits.

The issue is further complicated by the fact that it is difficult to assess whether or not a given condition in a child was caused by pertussis vaccine. Thus, parents of a child who has recently developed evidence of central nervous system (CNS) dysfunction and who has also recently received DTP vaccine may make an unwarranted assumption that the pertussis vaccine caused the CNS problem. If the manufacturer or provider of the vaccine does not agree, a polarization of views occurs as the parties adopt adversary positions. The polarization may be exaggerated if the parents' claim against the manufacturer or provider is denied.

**Influence of the media.** The ubiquity of the media, particularly the electronic media, makes it possible to bring into virtually every home a dramatic portrayal of the uncertainties and debate about pertussis and pertussis vaccine. The impact of such a portrayal is heightened by the very success of the vaccination program. In this country, there are presently very few instances of acute brain damage or deaths due to pertussis. Consequently, it is not possible to have a portrayal of the risks of the disease that is nearly as dramatic as portrayal of the risks of the vaccine.

The potential of the electronic media for impact on public attitudes toward, and acceptance of, vaccination is vividly demonstrated by the experience of the United Kingdom, where in 1974 dramatic television portrayals of children with brain damage thought to be due to pertussis vaccine led to a major decline in the acceptance of pertussis vaccine. This decline led to two major epidemics of pertussis in the United Kingdom—one in 1977–79, with more than 100,000 cases and 36 deaths, and the other in 1982, with more than 65,000 cases and 14 deaths.

In the United States, a 1-hour television program was shown in Washington, D.C., in April 1982, with subsequent nationwide coverage given a 15-minute segment of the program. The program vividly portrayed the risks known or alleged to be associated with pertussis vaccine, while minimizing or denying the benefits resulting from vaccination. The program has spurred some intensification of public interest in the subject as well as congressional attention. To date, however, it does not appear to have had a major impact on the overall utilization of pertussis vaccine.

Much of the evidence for the benefits of pertussis vaccination arises from epidemiologic studies regarding the incidence of the disease and the effectiveness of the vaccine in preventing it. The very nature of epidemiologic data has contributed to the controversy, since there is virtually no epidemiologic study with absolutely incontrovertible results that allow only one interpretation. Thus, epidemiologic methods play a very important role in developing public policy but cannot, by themselves, guarantee the acceptance or implementation of that policy.

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# Epidemiology: A Step Forward in the Scientific Approach to Preventing Cancer Through Chemoprevention

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**Synopsis**

*Until quite recently, the rigor and systematic approach applied to clinical research had never been applied to cancer prevention research. During 1982–83, however, the National Cancer Institute (NCI) carefully reviewed the needs and potentials in cancer prevention and control and developed a new policy for prevention research, requiring that development of cancer intervention follow an orderly sequence of research phases. These phases provide systematic assessment of interventions so that only those proven to be effective are brought to widespread implementation.*

*The author presents an overview of the new cancer prevention research policy; explains the manner in which epidemiologic studies contribute to development of policy and research; and describes NCI's research plan for chemoprevention, providing highlights of research studies that have contributed to its development and that will be implemented under the plan.*

At the National Cancer Institute (NCI) in the Division of Cancer Prevention and Control, we have recently taken a long, hard look at the concepts of prevention and control as they have been historically understood and applied. We found an important lesson for future cancer research in two examples, one negative and one positive.

The negative example is our short progress on the route to preventing lung cancer caused by cigarette smoking. Although research has established for at least two decades that the most effective means of preventing lung cancer is to eliminate cigarette smoking, only recently has a concentrated effort been made to develop policies to achieve that goal. We still lack knowledge about how to influence smoking behavior, especially among youths. Had we developed a strategy 20 years ago for ascertaining when a research base is adequate to support policymaking and information dissemination, and acted more forcefully on that strategy, we might have fewer deaths from lung cancer today.

The positive example is the clinical progress made in cancer therapy since the 1950s. A research strategy evolved, based on clinical trials as a means of evaluating the efficacy of treatments. Then, in 1955, the National Cooperative Chemotherapy Program was organized, ensuring participation of the best researchers in the nation, high standards, and compatibility of studies. As results became available, they were quickly communicated and