The Relationship Between Pertussis Vaccine and Central Nervous System Sequelae: Continuing Assessment

Reassessment of the role of whole-cell pertussis vaccine as a cause of permanent neurologic damage is necessitated by the 10-year follow-up of the National Childhood Encephalopathy Study (NCES) in Great Britain. The findings of this study demonstrate that infants and young children with serious acute neurologic disorders are at an increased risk of later neurologic impairment or death, irrespective of the initial precipitating event. The results, however, do not establish a causal relationship between pertussis vaccination and chronic neurologic abnormalities. The Academy reaffirms its earlier conclusion that whole-cell pertussis vaccine has not been proven to be a cause of brain damage and continues to recommend pertussis vaccination in accordance with the guidelines in the 1994 Red Book.1

In 1991, the American Academy of Pediatrics (AAP), on the basis of data that included findings from the NCES in Great Britain, concluded that whole-cell pertussis vaccine had not been proven to be a cause of permanent brain damage.2 The subsequent 10-year follow-up study of the NCES, however, provides additional data on the outcome of children whose initial acute neurologic illnesses were temporally associated with the administration of the diphtheria-tetanus-pertussis (DTP) vaccine and the possible role of pertussis vaccine in chronic central nervous system dysfunction.3 These findings were reviewed in 1994 by the Institute of Medicine (IOM) and subsequently by a subcommittee of the National Vaccine Advisory Committee (NVAC) in view of their relevance to vaccine safety and the then pending revisions of the Vaccine Injury Table by the National Compensation Program (which were subsequently issued in 1995).4 Accordingly, the relationship between DTP vaccination and chronic neurologic disorders has been reconsidered by the AAP.

THE NCES

The NCES, a large, case-control, population-based study from 1976 to 1979, examined the causes and natural histories of serious acute neurologic illnesses in children 2 to 36 months of age who were admitted to hospitals.3-6 The study population consisted of 1182 cases with two matched controls for each case. The possible causative role of whole-cell pertussis vaccine in these illnesses was examined by assessing the temporal association between immunization and the onset of the disorder. The investigators concluded that a significant association exists between the occurrence of acute neurologic illness (excluding infantile spasms) and DTP vaccination within the preceding 7 days. Of the 904 previously healthy children with acute neurologic illness whose immunization histories were known, 3.3% had received the DTP vaccine during the 7 days before the onset of illness (excluding infantile spasms) in comparison to 1.3% of the control children.5 The relative risk of DTP immunization in the cases was 3.3 (95% confidence interval [CI], 1.7 to 6.5).

The 1991 IOM committee that reviewed the adverse consequences of pertussis vaccine concluded that the evidence, including the NCES results, was consistent with a causal relationship between the DTP vaccine and acute encephalopathy as defined in the NCES and other studies.7 According to the IOM committee, the attributable risk in the NCES for serious acute neurologic illness (most commonly, prolonged febrile convulsions) in the week after DTP immunization in previously normal children was 6.8 per million doses administered (95% CI, 2.1 to 15.9 per million). The estimated risk for encephalopathy, ie, excluding other acute neurologic illnesses such as complex febrile seizures, was 2.7 per million doses of DTP (95% CI, 0 to 10.5 per million).

During the 10-year follow-up of children in the NCES, those who had serious acute neurologic illnesses in early childhood were significantly more likely to have the long-term adverse consequences of deafness and/or neurologic dysfunction, irrespective of whether they were temporally associated with DTP vaccination, than were matched control children who did not have acute neurologic illnesses.3 Neurologic abnormalities ranged from minor problems in vision and motor function to severe and multiple disorders, including epilepsy and impaired intellectual development. Although at follow-up, 77% of the children with acute encephalopathy had died or had neurologic dysfunction, only 24.2% of the control children did so. Of the 18 previously healthy children in whom neurologic illnesses developed within 7 days of DTP vaccination, 3 (16.7%) had died, and 9 (50%) had evidence of neurologic dysfunction at follow-up. However, the prevalence of death or sequelae (67%, 12 of 18 children) was similar to that in 576 children (62%) whose onset of acute neurologic illnesses were not temporally associated with DTP vaccination. Thus, any child who had an acute disorder was more likely to have chronic neu-
rologic dysfunction than a control child. The investigators, therefore, concluded that whole-cell pertussis immunization “may on rare occasions be associated with the development of severe acute neurologic illness that can have serious sequelae.” Furthermore, the role of DTP immunization as a prime or concomitant factor could not be determined in any individual case, and some cases may have occurred by chance or had alternative causes.

THE 1994 IOM COMMITTEE REVIEW

In the 1991 report concerning DTP vaccination and neurologic disorders, the IOM concluded that the data were insufficient to determine whether DTP was causally related to permanent neurologic damage. At that time, only the preliminary results of the 10-year NCES follow-up were available. After the follow-up data were published, however, the IOM committee concluded that the “balance of evidence is consistent with a causal relation between DTP and chronic nervous system dysfunction in children whose serious acute neurological illness occurred within 7 days of DTP vaccination.” The committee also noted that this association could be explained by one of the three following possibilities:

1. “DTP administration might cause serious acute neurologic illness and subsequent, chronic dysfunction.”
2. “DTP might trigger (and thereby be an immediate or precipitating cause of) an acute neurological illness and subsequent chronic dysfunction in children with underlying brain or metabolic abnormalities,” which otherwise might have occurred even in the absence of DTP vaccination in response to some other event; and
3. “DTP might cause an acute neurological illness in children with underlying brain or metabolic abnormalities that would themselves eventually have led to chronic nervous system dysfunction even in the absence of an acute neurological illness.”

These possibilities encompass a spectrum of causation ranging from a causal relationship (first possibility) between DTP vaccination and neurologic abnormalities to a noncausal association (third explanation). The second possibility suggests that DTP vaccination may cause the acute event, but it may not increase the overall risk of chronic nervous system dysfunction in vaccinated children. The IOM committee further concluded that the data in the NCES 10-year follow-up study were insufficient to determine which of these possibilities was most likely, and, thus, the findings were consistent with, but not proof of, a causal relationship between DTP vaccination and neurologic sequelae.

The committee also noted that the study concerns only the relationship between DTP vaccination and the onset of neurologic disorders in children who have serious acute neurologic illnesses within 7 days of vaccination and provides no evidence for a causal relationship in other circumstances.

THE NVAC AND ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP) REVIEW

An ad hoc subcommittee of the NVAC subsequently reviewed the IOM findings in view of their relevance to possible revisions of the Vaccine Injury Compensation Table. The committee concluded that “the data are insufficient to accept or reject that the DTP administration before the acute neurological illness influenced the potential of neurological dysfunction ten years later.” The ACIP of the Centers for Disease Control and Prevention has concurred with this assessment. Representatives of the AAP participated in the deliberations of both committees.

The ACIP further noted that the 10-year NCES follow-up study examined the risk of long-term neurologic dysfunction in those children whose acute illnesses occurred within 7 days of DTP vaccination. The ACIP added that the NCES findings on acute neurologic events demonstrate that the increased risk of initial illness occurs primarily in the first 3 days after vaccination. The statistical significance of the association of illness with DTP vaccination administered more than 72 hours but within 7 days of the onset of neurologic symptoms is less clear. Therefore, if DTP immunization influences the risk of chronic neurologic disorders, the risk is primarily in children who have acute neurologic events in the first 3 days after DTP vaccination.

ASSESSMENT BY THE COMMITTEE ON INFECTIOUS DISEASES

The long-term findings of the NCES indicate that serious acute neurologic illnesses in infants and young children are associated with an increased risk of chronic neurologic dysfunction in later childhood. The findings do not indicate whether the neurologic outcome is affected by the cause of the acute illness. Although the evidence is consistent with a causal relationship between whole-cell pertussis vaccination and serious acute neurologic disorders, these findings do not demonstrate conclusively that DTP vaccination is the cause of these temporally associated illnesses. For example, some neurologic disorders, such as infantile spasms, can be precipitated but not caused by DTP vaccination, as demonstrated by NCES findings reviewed in the earlier AAP statement. With infantile spasms, the relative risk of precipitation by DTP vaccination is increased in the interval immediately after vaccination but is decreased thereafter and for the total interval of 28 days after immunization is not increased. In a recent population-based, case-control pilot study in the United States of acute neurologic illnesses in children 1 to 24 months of age, a similar temporal relationship between the occurrence of encephalopathy and complex febrile seizures and DTP vaccination was noted. Whereas the risk of onset of these disorders within 7 days of DTP vaccination was increased, for those who received the vaccine at longer intervals after the onset of neurologic disorders, the risk was decreased, and the overall risk in the 28 days after DTP vaccination was the same as that for unvaccinated children. These authors concluded that, “al-
likely to have died or have had neurologic abnormalities 10 years later than children who did not have acute neurologic disorders, irrespective of the initial precipitating events. The results, although consistent with the conclusion that DTP vaccination can be associated with chronic neurologic dysfunction in children who earlier had severe acute neurologic illnesses after DTP vaccination, do not establish a causal relationship between vaccination and chronic neurologic disorders. The available data do not alter the earlier conclusions of the Committee on Infectious Diseases concerning the role of DTP vaccination in brain damage. Thus, the AAP concurs with the ad hoc subcommittee of the NVAC and the ACIP that whole-cell pertussis vaccine has not been proven to be a cause of brain damage. Pertussis immunization in accordance with the guidelines in the 1994 Red Book continues to be recommended. Specific guidelines for the use of acellular pertussis vaccines, however, will be revised upon FDA approval of one or more of these products for use in infants.

CONCLUSION
The findings of the 10-year NCES follow-up study demonstrate that infants and young children who have serious acute neurologic illnesses are more likely to have died or have had neurologic abnormalities 10 years later than children who did not have acute neurologic disorders, irrespective of the initial precipitating events. The results, although consistent with the conclusion that DTP vaccination can be associated with chronic neurologic dysfunction in children who earlier had severe acute neurologic illnesses after DTP vaccination, do not establish a causal relationship between vaccination and chronic neurologic disorders. The available data do not alter the earlier conclusions of the Committee on Infectious Diseases concerning the role of DTP vaccination in brain damage. Thus, the AAP concurs with the ad hoc subcommittee of the NVAC and the ACIP that whole-cell pertussis vaccine has not been proven to be a cause of brain damage. Pertussis immunization in accordance with the guidelines in the 1994 Red Book continues to be recommended. Specific guidelines for the use of acellular pertussis vaccines, however, will be revised upon FDA approval of one or more of these products for use in infants.

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REFERENCES
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