whose previous pregnancy resulted in an infant with early onset GBS disease, additional affected neonates are known to occur, although the exact risk is unknown. Because there is *some* risk, because of the great parental anxiety surrounding such pregnancies and because of unavailability of *proved* methods for preventing a second episode, intrapartum administration of either penicillin G (1.5 million units every 4 hours) or ampicillin (1 every 6 hours) given intravenously from the onset of labor or membrane rupture, whichever occurs first, is recommended. In the penicillin-allergic patient, a cephalosporin can be substituted. Treatment of the mother is discontinued at the time of delivery.

Q. On balance, what are the prospects for prophylaxis against GBS disease? Gaze into your crystal ball and tell us what you see.

A. Immunologic methods for prevention of GBS infection hold the greatest promise for the long term elimination of early onset disease and are the only methods aimed at late onset infections. The potential exists for passive immunization of women in labor or neonates at birth with gamma globulin preparations. Questions regarding the target population, the effective dose, the timing of administration, the potential risks and efficacy are all unanswered.

Strategies for active immunization of pregnant women including timing of administration, definition of a target population and a multicenter efficacy trial will be difficult, costly and time-consuming. However, the unique feature of active immunization of mothers as a method of preventing infection in the offspring is the possibility for "permanent" immunity in the adult and passive immunity in the neonate of sufficient duration (2 to 3 months) to offer protection throughout the age of susceptibility for both early and late onset GBS disease.

Definitive studies pertaining to efficacy of intrapartum chemoprophylaxis must be pursued in order to provide information on benefits *versus* risks incurred in exposing a large number of pregnant women to side effects of antibiotics.

While a great deal remains to be done in order to realize the prevention of GBS disease, the progress made in our understanding of the epidemiology and pathogenesis of these infections during the past decade should cause clinicians to be optimistic when thinking about the future.

0277-9730/83/0005-0006$02.00/0
PEDIATRIC INFECTIOUS DISEASE

Vol. 2, No. 1
Printed in U.S.A.

Sudden infant death syndrome, diphtheria-tetanus toxoid-pertussis vaccination and visits to the doctor: chance association or cause and effect?

VINCENT A. FULGINITI, MD

Temporal association is a powerful tool of the medical investigator. Often linkage of two events in sequence provides the first clue to etiology; i.e. Event A is associated with Event B which comes later, and subsequently the two are tied together in the pathogenesis of Event B. But as powerful a tool as it is, temporal association can be misleading in medicine. Event A can precede Event B but be totally unrelated to it, as a third factor operates to produce the temporal sequencing, or chance results in the apparent association.

The report by Baraff et al.[1] in this issue points out this epidemiologic dilemma. They demonstrate a temporal relationship between diphtheria-tetanus toxoid-pertussis vaccine (DTP) administration and sudden

Address for reprints: Vincent A. Fulginiti, M.D., Department of Pediatrics, The University of Arizona Health Sciences Center, Tucson, AZ 85724.

infant death syndrome (SIDS) and between visits to a physician without receipt of DTP and SIDS. Among the facts presented are: (1) only 38% of 382 SIDS were evaluated; (2) 53 infants of 145 evaluated received DTP, 11% within 1 day, 32% within 1 to 7 days and 51% within 4 weeks of DTP; (3) 46 infants of the 145 had visited a physician without receiving DTP, 9% within 1 day, 40% within 1 to 7 days and 87% within 4 weeks; and (4) there were no controls.

What is the relationship between these A's and B? The answer to this question is difficult to assert with certainty. I will test this hypothesis by using epidemiologists' criteria for causality of a temporal association by asking five questions. (This analysis is usually applied to the case-control type of study.) These five criteria, in the form of questions, give some estimate of the reasonableness of a causal hypothesis.

1. Are the results of this study consistent with others exploring the same relationships? The CDC has analyzed its assessment of a possible DTP/SIDS relationship in Tennessee.[2, 3] The authors discuss this analysis in detail; the CDC concludes there is no causal association. Dr. William Torch, a pediatric neurologist, presented his study in Nevada recently at a national meeting.[4] This engendered considerable discussion; his study purported to show a relationship. NIH investigators in the audience presented preliminary data from a controlled national collaboration study which showed no correlation.[5] Finally countries which defer DTP to 6 months have an identical pattern of SIDS prior to 6 months.[6]

2. Has chance been excluded? The authors utilized a "reasonable" comparison in lieu of controls to demonstrate that DTP was significantly associated with SIDS; i.e. chance was unlikely to cause it. They calculated expected deaths by assuming no relationship with DTP and distributing deaths among each age interval on an equal basis for each day of the month. This is a valid statistical device but dubious as a comparison in my view. Their assumption is that clustering of cases post-DTP assumes significance if one "expects" deaths to occur evenly on a daily basis.

3. How strong is the association? The stronger it is, the more likely is it to be causal. We cannot tell how strong it is from present data. There is no test that will do since there is no actual control group. The tests of significance are distributed oddly among the time intervals (Table 2 in their text): very high significance (i.e. low chance effect) at less than 1 day, weak at 4 to 7 days and moderate at 22 to 28 days post-DTP; no significance (i.e. no better than chance) on Days 2, 3, 8 to 14 and 15 to 21. Similar analyses pertain to visits to the doctor (Table 3 in their text). It is difficult to explain these variances except possibly by chance or by the inappropriateness of the method used.

4. Is the association biologically credible? The answer is a clear yes. DTP (P) can cause sudden collapse and shock (hypotonic, hyporesponsive syndrome) and has resulted in almost immediate death in the rare individual. There is no reason to doubt a possible cause-effect relationship (also see authors' discussion).

5. Is there a dose response? This cannot be assessed because the mechanism of SIDS is unknown and the dose of DTP is constant by volume but is unknown by specific constituent on a weight per kg body weight basis for each and every dose and child.

What can we conclude from these data? The authors said it as well as anyone, " ... this study is a preliminary effort with only provisional findings," and, "these findings may not be substantiated in more carefully controlled studies."

In the search for biologic truth we must not disregard or scorn potential clues to enlightenment. This study and others like it should be neither discarded nor *quoted as proof.* They serve as possible hypotheses for others to challenge or extend. In summary we do not know what causes SIDS; we do not know if DTP does. We should attempt to find out; it is not a trivial question.

REFERENCES

1. Baraff LJ, Ablon WJ, Weiss RC: Possible temporal association between diphtheria-tetanus toxoid-pertussis vaccination and sudden infant death syndrome. *Pediat Infect Dis* 2:7–11, 1983
2. CDC: DTP vaccination and sudden infant deaths—Tennessee. *Morbid Mortal Weekly Reports* 28:131–132, 1979
3. CDC: Follow-up on DTP vaccination and sudden infant deaths: Tennessee. *Morbid Mortal Weekly Reports* 28:134–136, 1979
4. Torch W: Diphtheria-pertussis-tetanus (DTP) immunization: A potential cause of the sudden infant death syndrome (SIDS). *Neurology (NY)* 32:A169–A170, 1982
5. Cooperative epidemiological study of SIDS risk factors. NIH Press Release, National Institute of Child Health and Development, Office of Research Reporting, May 3, 1982
6. CDC: Diphtheria, tetanus and pertussis: Guidelines for vaccine prophylaxis and other preventive measures. *Morbid Mortal Weekly Rep* 30:392–396, 401–407, 1981