Ronald Gold

# Pertussis: The Disease and The Vaccine


## SUMMARY

Pertussis still causes significant morbidity: average duration of the illness is six to eight weeks. Almost one third of infants have complications including weight loss, apneic spells, otitis media, pneumonia, and seizures. Encephalopathy occurs in approximately one in 2000 infants: one third die and one third sustain permanent brain damage. The mortality rate is one in 1000 infants. Pertussis vaccine consists of heat and formalin-killed whole bacteria. Minor reactions of fever, irritability, crying, and local reactions occur after 40-60% of injections. Major reactions include prolonged screaming, seizures, collapse, fever over 40.5°C, and encephalopathy. Permanent brain damage occurs in association with one in 310,000 injections, so the benefits clearly outweigh the risks. All young children should be immunized. (Can Fam Physician 1986; 32:79-83.)

## SOMMAIRE

La coqueluche est encore responsable d'une morbidité significative: la durée moyenne de la maladie va de six à huit semaines. Jusqu'à 30% des enfants présentent des complications comprenant perte de poids, périodes d'apnée, otite moyenne, pneumonie et convulsions. L'encéphalopathie survient chez environ 1 enfant sur 2,000; le tiers en meurent et un autre tiers souffrent de dommages cérébraux permanents. Le taux de mortalité est de 1 pour 1,000 enfants. Le vaccin contre la coqueluche est fabriqué à partir de bactéries complètes, tuées par la chaleur et la formaline. Quarante à soixante pourcent des injections provoquent des réactions mineures de fièvre, irritabilité, pleurs et certaines réactions locales. Par contre, les réactions majeures incluent des pleurs prolongés, des convulsions, un collapsus, une température supérieure à 40.5°C et une encéphalopathie. Les dommages cérébraux permanents surviennent dans 1 injection sur 310,000; les bénéfices dépassent donc largement les risques. Tous les jeunes enfants doivent être immunisés.


**Key words:** Pertussis, vaccine, prevention

**Dr. Gold is professor of pediatrics at the University of Toronto, and chief of the Division of Infectious Disease at The Hospital for Sick Children. Reprint requests to: The Hospital for Sick Children, 555 University Avenue, Toronto, ON. M5G 1X8.**

BEFORE 1945, large epidemics of pertussis occurred in Canada, with a peak of 19,484 cases in 1934.[1] Following the introduction of a combined diphtheria toxoid-pertussis vaccine in 1943, the incidence of pertussis declined significantly. Currently, approximately 2000 cases are reported annually, a 93% decrease from the prevaccine period.

Pertussis has always been considered a disease of infancy and early childhood,[2] which may reflect the fact that the disease is more severe and easier to recognize in the young. Recent studies utilizing very sensitive antibody assays to supplement cultures in diagnosis have demonstrated that infections in older children and adults are very common, although they are more likely to be mild or asymptomatic. In a study of the spread of pertussis within families, Mertsola et al. found that the secondary attack rate in infants was 100%, compared to 85% in children two to 15 years of age and 80% in parents.[3] However, only 40% of adults had symptoms compared to 90% of infants. The occurrence of infection in older children and adults means that early childhood immunization does not eliminate the bacteria from the community, but does protect the age group most vulnerable to severe illness and complications.

Pertussis typically has three stages.[2,4] In the first, or catarrhal stage, the disease begins as an ordinary upper respiratory infection with a profuse nasal discharge and mild cough. Fever is unusual. After one or two weeks, the paroxysmal stage begins, characterized by the sudden, unexpected occurrence of severe paroxysms of coughing. Each attack consists of 10-30 coughs followed by a very forceful inspiration which may produce the whoop for which the disease is named. Initially the paroxysms are more common at night, but as they become more frequent, they occur just as often during the day, averaging 15 paroxysms per day. Approximately 25% of infants will have more than 20 spells per day.[5] Cyanosis during paroxysms is extremely common and 75% of patients will vomit after an attack. The paroxysmal stage lasts two to four weeks and is followed by four to 12 weeks of convalescence.[6]

Complications of pertussis are most common and most severe in infants, especially in those under six months of age.[7] Most studies of the morbidity and complications of pertussis have examined only children sick enough to be hospitalized.[8-12] A more useful approach is exemplified by a recent study of all 2295 clinically confirmed cases reported during the 1977-79 epidemic

in West Glamorgan, a city of 360,000 in Wales where less than 10% of young children were immunized.[4, 13] All 212 general practitioners in the city cooperated in the study by reporting cases to the Area Health Authority by telephone. On the same day, a public health nurse visited the home, completed a questionnaire, and obtained pernasal swabs on each member of the household with symptoms.

Whooping occurred in 45% of patients, cyanosis in 19%, and vomiting after coughing in 66%. Only 64 (2.8%) of the 2295 cases were hospitalized. However 63 were under age three; in this age group the hospitalization rate was 12%. The type and frequency of complications are listed in Table 1.

In a study of 8092 cases, Miller and Fletcher found that 28% of patients had one complication or more.[14] The frequency of complications in hospitalized and non-hospitalized patients is summarized in Table 2. Clearly, even with modern medical care, pertussis still causes serious illness. No specific treatment is yet available.

## Pertussis Vaccine

Pertussis vaccine consists of a suspension of whole cells of Bordella pertussis which have been killed by heat and formalin. Thiomersal is added as a preservative. The vaccine is usually administered in combination with diphtheria and tetanus toxoids which have been adsorbed on to aluminum phosphate. In provinces using killed polio vaccine, a combined DPT-polio is used.

Before 1981, fluid or plain vaccines were utilized in Canada. It is unknown whether the tenfold higher incidence of reported cases in Canada compared to that in the United States in 1982-83 was a result of differences of efficacy of the Canadian fluid vaccine compared to the American adsorbed vaccine or to differences in rates of reporting cases.[1, 15] Vaccines containing aluminum salts as adjuvants are superior to fluid vaccines because they induce higher and more sustained antibody concentrations,[16, 17] thereby necessitating fewer booster doses. In addition, local and systemic adverse reactions occur significantly less often after adsorbed than after fluid vaccines.[17, 18]

B. pertussis is a Gram-negative bacteria containing a variety of toxic substances including endotoxin, pertussis toxin (PT), fimbrial hemagglutinin (FHA), adenyl cyclase, and heat labile dermatotoxin.[19] Animal studies have shown that virulence is related to PT, FHA, and adenyl cyclase. Obviously, therefore, a vaccine composed of killed, whole bacterial cells frequently produces adverse reactions. Minor reactions occur in 40-60% of recipients and include fever, irritability, crying, drowsiness, and redness, swelling, pain, and tenderness at the injection site.[20-21] All of these reactions also occur after DT vaccine without pertussis vaccine, but at an incidence of 10-25%.[20, 22]

## Reactions to Pertussis Vaccine

Severe reactions to pertussis vaccine are rare. They include very high fever (>40.5 C), prolonged screaming, collapse, convulsions, acute encephalopathy, permanent brain damage, and systemic allergic reactions. Most convulsive episodes consist of a tonic-clonic seizure usually associated with high fever and lasting less than ten minutes. About 60% of seizures occur within 12 hours and almost all within 48 hours of vaccination.[20, 23, 24] No permanent neurologic sequellae have been observed after these brief seizures,[20, 25, 26] for which the incidence is one per 1750 immunizations.[20] Seizures lasting over 30 minutes occur much less frequently. Prolonged, generalized seizures of any etiology may cause brain damage.[27]

Collapse or shock-like reaction occurs in one of 1750 immunizations.[20] Usually within six hours of receiving pertussis vaccine, the infant suddenly becomes very pale, hypotonic, and unresponsive. The symptoms last less than one hour in about 45% of infants, but up to 24 hours in the remainder. No permanent sequelae have been described after the collapse reaction.

Persistent crying lasting more than three hours during which time the infant cannot be comforted occurs in approximately 1% of infants.[20] Persistent screaming with a high pitched, abnormal cry occurs after one per 1000 immunizations. The significance of this reaction is unknown.

Acute encephalopathy and permanent brain damage following administration of pertussis vaccine is a very rare event. The National Childhood Encephalopathy Study analyzed the immunization histories of 1182 children under age three who were hospitalized in England and Scotland with acute, severe neurologic illnesses of unknown etiology.[27] Histories were obtained while the children were still hospitalized, and compared to two controls matched for age, sex, and place of residence. Only 3.5% of the pertussis patients had received pertussis vaccine within seven days of becoming ill, and they were twice as likely to have received pertussis vaccine in the week before admission as were the controls. The frequency of immunization for patients and controls was the same during the two to four weeks before onset. The risk of acute neurologic illness severe enough to require hospitalization was one per 110,000 injections. The risk of permanent neurologic sequelae being present

**TABLE 1**
**Percentages of Complications after Pertussis During 1977-79 Epidemic in West Glamorgan, Wales**

| Complication | Frequency |
|---|---|
| Weight loss | 16.8 |
| Bronchitis | 9.8 |
| Otitis media | 7.5 |
| Pneumonia | 0.8 |
| Convulsions | 0.6 |
| Atelectasis | 0.3 |
| Hernia | 0.1 |
| Death | 0.1 |
| Encephalopathy | 0.09 |

**TABLE 2**
**Percentage Frequency of Complications Occurring in 8092 Cases of Pertussis in the United Kingdom, 1974-75**

| Complication | Hospitalized (n=775) | Non-Hospitalized (n=7317) |
|---|---|---|
| Pneumonia | 18.0 | 2.0 |
| Apnea | 5.0 | 0.5 |
| Convulsions | 4.0 | 0.05 |
| Death | 1.1 | 0 |
| Encephalopathy | 0.3 | 0 |

one year later was one per 310,000 injections of DPT.

Infantile spasms have also been linked to pertussis vaccine, but results of the National Childhood Encephalopathy Study and of studies in Denmark provide strong evidence against the existence of any causal relationship between pertussis vaccine and infantile spasms.[28, 29]

Comparisons of the risks of permanent brain damage which is temporally associated with the disease and with the vaccine are difficult because both are rare events.[7] A long-term, prospective study of children born in England, Scotland, and Wales during the week of April 5-11, 1970 has been undertaken.[30] Children who had not been immunized against pertussis were more likely to have had convulsions, speech defects, and lower scores on intelligence tests than were children who had received pertussis vaccine. Forty children in the cohort had had pertussis by age five; they had significantly higher rates of speech disorders, poor school performance, and lower intelligence scores than did immunized children.

If the risk of permanent brain damage after pertussis vaccine is one per 310,000 injections,[27] what is the risk of brain damage after pertussis in infancy? During recent epidemics in the United Kingdom, the incidence of pertussis was approximately 20 per 1000 infants. The risk of encephalopathy was approximately one per 400 cases of pertussis in infants under age two;[4, 7] therefore the risk of encephalopathy during epidemics is approximately one per 2000 infants. One third of infants with pertussis encephalopathy die, one third survive with permanent brain damage, and one third survive intact.[31, 32] The risk of brain damage associated with the vaccine is therefore far less than that caused by the disease.

Another condition attributed to pertussis vaccine is sudden infant death syndrome. Two small studies with incomplete follow-up of cases and no controls found a temporal association between recent pertussis vaccine and SIDS.[33, 34] In addition, four cases of SIDS occurred in Tennessee within 24 hours of pertussis vaccination.[35] A large, multicentre, case-control study has found no evidence to confirm even a temporal association between pertussis vaccination and SIDS.[36] Analysis of the first 400 cases of SIDS and 800 controls (400 matched for age and 400 matched for age, race, and birth weight) found that SIDS patients were significantly less likely to have received DPT than were controls (39% versus 56%). Only 1% of cases had received pertussis vaccine in the preceding 24 hours, compared to 2% of controls.

Thus, in spite of the reactions which occur after the use of pertussis vaccine, it is clearly much safer to immunize infants and young children than to allow them to contract pertussis.[7]

Does pertussis vaccine prevent disease? Controlled field trials in the United States and the United Kingdom demonstrated the vaccine to be 80-85% effective in preventing disease following household exposure.[2, 7] Cases in fully immunized children were mild. Implementation of mass immunization programs of infants and young children was followed by significant declines in the incidence of pertussis in Canada,[1] the USA,[7] the United Kingdom,[37-39] Japan,[40] and many other countries. Recent estimates of vaccine efficacy in the United States found that the current vaccine prevents 94% of cases following household exposure.[41] Several recent reviews have clearly demonstrated that the benefits of vaccine far outweigh the risks.[7, 42-44]

The efficacy of pertussis vaccine was further demonstrated in the United Kingdom and Japan. Refusal of parents to allow their children to be immunized because of fears aroused by exaggerated mass media accounts resulted in major declines in pertussis immunization rates. Both countries subsequently experienced major epidemics.[7, 37, 40] Analysis of the 1977-79 epidemic in the United Kingdom indicated that there was a highly significant negative correlation ($p<0.001$) between immunization rates and disease incidence.[45] Areas with low immunization rates had nearly twice as much pertussis as did areas with high immunization rates.

## DPT, Adsorbed And DPT-Polio, Adsorbed Vaccines

Unlike fluid vaccines which are injected subcutaneously, adsorbed vaccines must be administered intramuscularly. The preferred site in infants is the mid-portion of the anterolateral thigh because of the large muscle mass and absence of major vessels or nerves. A one inch, #23-25 gauge needle is less likely to result in inadvertant subcutaneous injection than is a 0.5 inch #25 gauge needle. If the adsorbed vaccine is injected subcutaneously, large local reactions may occur.[46] Pertussis vaccine is not recommended for children over age seven because severe disease is rare in older children.

Reduced doses of vaccine have been shown to result in less frequent minor local and systemic reactions.[47] However there is no evidence that smaller doses will cause fewer severe reactions and therefore such schedules cannot be recommended.

Recent data support the recommendation that primary immunization of premature infants with DPT should begin at age two months.[48]

## Contraindications to Pertussis Vaccine[49, 50]

Contraindications to the use of pertussis vaccine include:

1. A major reaction to a previous dose of vaccine, e.g.

—acute encephalopathy, a severe neurologic illness without demonstrable cause characterized by severe alteration of consciousness, generalized and/or focal neurologic signs, and seizures.

—persistent, unconsolable screaming for over three hours.

—collapse reaction.

—fever greater than 40.5°C unexplained by other causes within 24 hours of vaccine.

—convulsion within 48 hours of vaccine.

—systemic allergic reaction.

2. An evolving neurologic disorder including uncontrolled seizures.

3. Personal history of convulsions. Infants with previous convulsions may be more likely to develop a convulsion after receiving pertussis vaccine, although confirmation of this risk awaits convincing data. Most authorities recommend that pertussis vaccine be deferred in infants with seizures until the disorder is controlled or stabilizes.[50]

Conditions which are *not* contraindications to the use of pertussis vaccine include: personal or family history of allergy, family history of seizures, and presence of upper respiratory infection. Such conditions are not associated with increased risks of adverse reactions. If a child has a febrile illness, it is reasonable to defer

immunization so that vaccine reactions do not obscure observation of the natural course of the illness.

## Prospects for the Future

Much has been learned about the pathogenesis of pertussis and the identity of the bacterial antigens responsible for inducing protective antibodies in the past few years.[19] Two proteins on the bacterial surface have been shown to be necessary for virulence: pertussis toxin (PT) and filamentous hemagglutinin (FHA).[51-53] Antibody to PT induced by vaccine or passively supplied protects mice against intracerebral and aerosol challenge. Antibody to FHA by itself is not protective, but augments the effect of anti-PT. PT has profound effects on a wide variety of cell types because it impairs regulation of intracellular concentration of cyclic nucleotides.[54] PT is an enzyme which specifically inactivates a regulatory protein in the host cell membrane. Consequently, cyclic-AMP accumulates within cells, resulting in derangement of cell function. Children receiving pertussis vaccine have impaired cardiovascular responsiveness to isoproterenol and epinephrine,[55] increased insulin activity in the blood,[56] increased sensitivity to carotid stimulation,[57] and other manifestations of impaired regulation of the autonomic nervous system.

An acellular vaccine composed of partially purified PT and FHA has been developed in Japan.[43] The vaccine is almost free of endotoxin activity. The pertussis toxin has been inactivated with formalin. In animal models, the component vaccine has significantly less activity on the autonomic nervous system than does whole cell vaccine.[58] Fever and local reactions occurred much less frequently in children given the new vaccine compared to standard pertussis vaccine.[43] Antibodies to both PT and FHA are induced in children. The new vaccine provided 80% protection against disease following household exposure,[59] but further experience is required to determine its safety and efficacy. Nevertheless, its development gives hope that a new and improved pertussis vaccine will soon be available. ◉

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