Microbe

FEATURES

Perspective

Historical Perspective on Pertussis and Use of Vaccines To Prevent It

100 years of pertussis (the cough of 100 days)

James D. Cherry

Unlike many other severe epidemic infectious diseases, pertussis lacks an ancient history. Perhaps the earliest mention of pertussis, or whooping cough, is of a 1414 outbreak in Paris in Moulton's *The Mirror of Health*, published in 1640. A contemporary observer, Guillaume de Baillou, described a 1578 epidemic of pertussis in Paris and, by the middle of the 18th century, pertussis was well recognized throughout Europe.

Carl Burger at University of Bonn, Germany, apparently recognized *Bordetella pertussis* in stained films of sputum by 1883, based on his drawings of elliptical rods. Other observations of bacilli in respiratory mucus followed, including Jules Bordet and Octave Gengou who in 1900 described finding a new "ovoid bacillus" in the sputum of a 6-month-old infant with whooping cough. They were also the first to cultivate the causative agent at the Pasteur Institute in Brussels in 1906.

Before pertussis vaccines became available, this disease caused a staggering amount of morbidity and mortality. U.S. use of vaccines to protect against pertussis from the 1940s to 1984 reduced the incidence of reported disease by more than 157-fold. Nonetheless, *B. pertussis* continues to circulate, with adolescents and adults serving as a reservoir for this pathogen. In general, the older, whole-cell-based pertussis vaccines have greater efficacy than do the newer acellular vaccines, but the former are also more reactogenic. An important advantage of the acellular vaccines is that because of their lessened reactogenicity they can be given to adolescents and adults, which will lead to the better control of pertussis.

Summary

- Although early pertussis vaccine use in the United States sharply reduced reported disease by more than 157-fold, the disease has been on the rise for the past two decades—in part because of decreased vaccine use.
- Current treatments for pertussis involve supportive care, avoiding factors that provoke coughing attacks, and paying careful attention to provide patients with fluids and nutrition.
- What was called pertussis-vaccine encephalopathy proved instead to be seizures attributable to infantile epilepsy; importantly, pertussis vaccine does not cause such illnesses.
- Several acellular pertussis—typically, combined with diphtheria and tetanus—vaccines that are now licensed appear to be safe and effective not only for infants but also for adolescents and adults.

Clinical Microbiology Practices Past and Present

During much of the first half of the 20th century, *B. pertussis* was cultured using Bordet-Gengou (BG) medium. Specimens typically were collected by the "cough plate" technique in which an agar plate was held within 3 to 6 inches of a child's mouth during a coughing spell. Although this technique was being used when I became a pediatric house officer in 1957, William L. Bradford and Betty Slavin earlier showed that nasopharyngeal (NP) swabs were more effective for culturing this pathogen.

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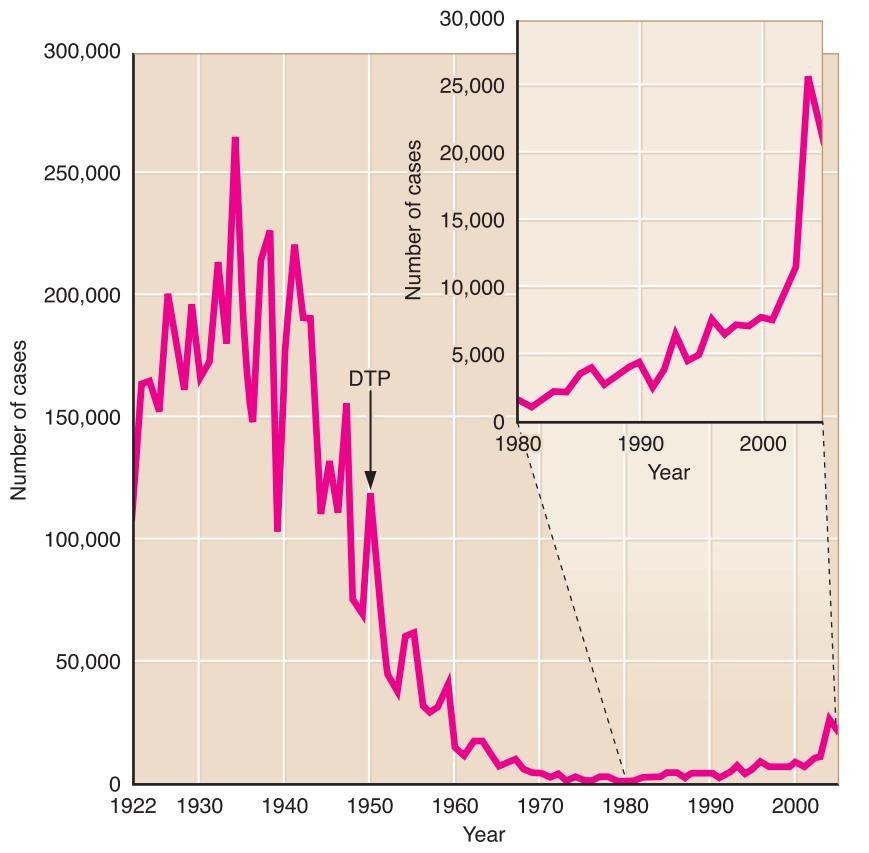
FIGURE 1



Pertussis cases in the United States, 1922–2005, based on data from the Centers for Disease Control and Prevention.

Several serologic tests were used during that period, including agglutination, complement fixation, and opsonocytophagic tests. Among them, complement fixation was the best. Early in the illness, it was negative; then it gave a peak titer in four to nine weeks, but fell to a nonmeasurable value in five to eight months. The opsonocytophagic test measured the uptake of organisms in neutrophils when incubated with antibody-containing sera. The test was appealing but nonspecific.

Laboratory diagnosis today relies on culture, but Regan-Lowe agar is used more often than BG medium because of its longer shelf life. Material for culture is obtained by NP swab or aspirate. When the swab or aspirate comes in contact with ciliated epithelial cells of the nasopharynx in children who have had a paroxysmal cough for two weeks or less, the sensitivity is about 80%.

Many laboratories throughout the United States are replacing culture with PCR tests. This test, which often uses insertion sequences in the genome of *B. pertussis* and *B. parapertussis*, is generally more sensitive than culture, but false positives can be a problem. The biggest advance during the last two decades has been development of ELISA techniques to measure immunoglobulin G (IgG) or IgA antibodies to pertussis toxin (PT). This approach facilitates the diagnosis of pertussis in adolescents and adults because such individuals rarely seek care until the third or fourth week of the illness, when cultures and PCR tend to be negative. Moreover, because virtually all adolescents and adults previously have had *B. pertussis* infections or were immunized, they typically have high antibody titers early in illness, making single-serum diagnosis very reliable.

Clinical Pertussis Has a Rich History

Pertussis typically occurs in three stages—catarrhal, paroxysmal, and convalescent—and lasts 4–12 weeks. Specific manifestations include a paroxysmal cough, lack of significant fever, no systemic illness, profuse nasal discharge but no significant pharyngitis, vomiting, whoop, and leukocytosis with absolute lymphocytosis.

Based on L. Emmett Holt's 1902 textbook, clinical pertussis remains remarkably constant. However, symptoms were more pronounced and hemorrhagic complications tended to be more frequent a century ago. Moreover, during summer outbreaks, infants with pertussis nearly always also had diarrhea, and those who experienced severe vomiting often developed malnutrition.

"No disease has a greater list of remedies proposed and enthusiastically lauded as 'specifics' than pertussis," noted Alfred Friedlander, Professor of Medicine, College of Medicine, University of Cincinnati, in 1925. For example, Holt recommended treating pertussis with fresh

air, a sea voyage, small formalin lamps to prevent reinfection, and alcohol stimulants. He also suggested insufflation with quinine or benzoic acid mixed with bicarbonate of sodium, talcum, or coffee; application by spray or swab of resorcin and carbolic acid; and inhalations with carbolic acid, creosite, and cresolene or chloroform. Additionally, he mentioned several drugs, including quinine, belladonna, bromoform, antipyrine, codeine, chloral, trional, and heroin.

Meanwhile, Friedlander suggested a tight abdominal binder to control vomiting. For specific treatment, Friedlander recommended vaccine therapy, including vaccines prepared with whole organisms or vaccine fractions containing undenatured bacterial antigen, topagen, and detoxified antigen. He also mentioned the use of high-titered animal serum and adult hyperimmune convalescent sera. Joseph H. Lapin, Adjunct Pediatrician, Bronx Hospital and Associate in Contagion, Riverside Hospital for Contagious Diseases, New York City, suggested paying particular attention to diet and hygienic measures, and he also suggested treating pertussis patients with X-rays, UV rays, climatotherapy, airplane trips, inhalations, insufflations, and laryngeal sprays.

Although today the treatment of pertussis does not involve many of those more dubious recommendations, it still suffers from lack of effectiveness. The mainstay of supportive care is avoiding factors that provoke coughing attacks, including a noisy environment, unnecessary examination, strangers, excessive brightness of room lighting, noxious odors, and the supine position. Careful attention to fluids and nutrition is important. Although corticosteroids and salbutamol are often used, their benefits are not demonstrated.

Hospitalized young infants should receive gentle suction and well-humidified oxygen. In general, infants with respiratory and cardiovascular failure due to pulmonary hypertension respond poorly to treatment. In such severe cases, patients are treated with pulmonary artery vasodialators and extracorporeal membrane oxygenation (ECMO). According to a recent hypothesis, pulmonary hypertension in very young infants is due to excessive leukocytosis with lymphocytosis. On this basis, some patients are being treated with double-volume exchange transfusions.

Vaccine Use Changed the Epidemiology of Pertussis

Before vaccines were available, reported pertussis occurred with an average rate of 157 cases per 100,000 population, high death rates, and peaks of illness every two to five years. One peculiarity of the clinical history of pertussis is that cases were more common among girls than boys, unlike many other infectious diseases that tend to predominate in boys.

The toll of pertussis before vaccines was staggering. For example, from 1926 to 1930, there were 36,013 pertussis-related deaths in the United States. The average death rates from 1940 to 1948 per 100,000 population per year were 64 in children less than 1 year old, 6.4 in those 1–4 years of age, and 0.2 in those 5–14 years of age. More than 90% of the reported pertussis cases occurred in children less than 10 years of age, with about 10% of those in children less than 1 year of age.

By 1974, extensive use of vaccines decreased the average annual incidence of reported pertussis to less than 1 per 100,000 population. Although 90% of those cases still occurred among children, the distribution shifted so that more than 50% occurred among those less than 1 year of age. However, by 2004, 66% of the reported cases occurred in those older than 10 years.

During the last 22 years there has been an increase in reported pertussis in the United States, peaking in 2004 at 25,827 cases. While this increase is alarming, it should be noted that we still have 10- to 15-fold fewer cases of reported pertussis today than we had in the prevaccine era. There have been a number of suggestions for possible reasons for this "resurgence" of reported pertussis. These suggestions include genetic changes in *B. pertussis*, lessened potency of pertussis vaccines, waning of vaccine-induced immunity, greater awareness of pertussis, and the general availability of better laboratory tests. It seems apparent to me that this increase is mainly due to the greater awareness of pertussis now than two decades ago. Also, in some states better diagnostic laboratory tests are available. Another factor which may be contributing to the increase of reported pertussis is the fact that in general the new acellular vaccines (DTaP vaccines) are not as efficacious as the former whole-cell DTP vaccines. This may

have contributed to the recognition of more recent cases in adolescents.

Of particular importance to me is the fact that the epidemiology of reported pertussis is vastly different from the epidemiology of *B. pertussis* infection. Over the last 20 years a number of studies have been done to delineate the epidemiology of *B. pertussis* infection. Here is a summary of these findings:

- *B. pertussis* infections in adolescents and adults are very common and endemic in the present vaccine era.
- Data from Germany in the early 1990s, when few children were being immunized and pertussis was epidemic, as well as much earlier observations in the United States, suggest that infections in adolescents and adults were common and endemic in the prevaccine era.
- Rates of reported pertussis are 40- to 160-fold less common than actual infection rates.
- Asymptomatic infections are 4–22 times more common than symptomatic infections.
- Today symptomatic adolescents and adults are the major source of infection in unvaccinated children.

Chaos in Formulating, Using Early Pertussis Vaccines

Pertussis was such a devastating disease in early infancy that soon after *B. pertussis* was isolated, many investigators made and tested a range of candidate vaccines, including whole-cell preparations that were washed or unwashed, mixed vaccines containing other respiratory tract flora, extracted vaccines, detoxified vaccines, and vaccines enriched with "toxic factors."

As early as 1923 some protection was noted in vaccine trials; however, the state of available vaccines was in such chaos that pertussis vaccines were withdrawn from new and nonofficial remedies. In the 10-year period from 1933–1942, there were many candidate vaccines and a number of these were shown in clinical trials to be efficacious. By 1944, pertussis immunization was endorsed by the American Academy of Pediatrics.

In the 1930s the following types of pertussis vaccines existed: whole-cell preparations which were washed or unwashed, mixed vaccines containing other respiratory tract flora, fractionated vaccines (extracted vaccines), detoxified vaccines, and vaccines enriched with "toxic factors." At this time the only toxin that had been identified was dermonecrotic toxin, which was heat labile, and therefore detoxification was easy.

It was realized relatively early that a good antibody response and clinical protection following immunization depended upon the number of organisms in the vaccine, and because of toxicity, there was a limit to the number of organisms that could be given in a single dose. Many of the early vaccines contained substantial amounts of human or animal serum, and immunization schedules included six or seven injections over a 2- to 3-month period to obtain a significant dose.

Almost from the outset, pertussis vaccines were associated with problematic side effects and temporally related severe events. For example, Thorvald Madsen, State Serum Institute, Copenhagen, Denmark, reported in 1925 that two neonates died after receiving the second dose of a pertussis vaccine during the first week of life.

Pertussis Vaccines Repeatedly Scrutinized for Safety

Concern about severe temporally related events (so called vaccine encephalopathy and sudden infant death syndrome [SIDS]) lead to a number of observational studies shortly after vaccine use became widespread. In 1948, Randolph K. Byers and Frederic C. Moll of the Department of Pediatrics, Harvard Medical School, and Infants and Children's Hospital, Boston, published a report of 15 children with severe neurologic disease which had its onset following immunization. This was followed in 1958 by a series by J. M. Berg, Fountain Hospital, London, with 107 cases and in 1974 by M. Kulenkampff, J. S. Schwartzman, and J. Wilson, The Hospital for Sick Children, Great Ormand St., London, who noted 36 cases. This latter uncontrolled study led to considerable media attention in England, and immunization use dropped precipitously, resulting in epidemic disease in 1977.

The next group of studies were those that attempted to determine a rate of severe neurologic disease ("vaccine encephalopathy") following immunization. Justus Ström of the Hospital for Infectious Diseases, Stockholm,

Sweden, published reports in 1960 and 1967 with very alarming results. Following this in 1977 Gordon Stewart in Glasgow, Scotland, suggested the rate of severe encephalopathy was 1 per 54,000 children. It is important to note that in none of these studies was there control for temporally related events due to other causes.

In 1978 and 1979, our group carried out an extensive study involving more than 16,000 children which looked comparatively at the rates of reactions following DTP vaccines versus DT vaccines. This study showed that redness, swelling, and pain at the injection site and fever, drowsiness, fretfulness, vomiting, anorexia, and persistent crying were all significantly related to the pertussis component of the vaccine. In addition, we noted the occurrence of hypotonic-hyporesponsive episodes, febrile convulsions, and high-pitched unusual crying in association with DTP vaccine.

Concern about these severe temporally related events led to decreased use or stoppage of immunization in England, Sweden, and Japan and subsequent epidemics of disease occurred in all three countries. In the United States there was considerable media coverage that in contrast to England, Sweden, and Japan, had little detrimental effect on vaccine usage, but did result in an epidemic of DTP lawsuits. At this time it was pointed out by my close friend and colleague, Ted Mortimer of Case Western Reserve University, Cleveland, Ohio, that "subsequences and consequences are not synonyms." As an example he said that "some people who go outside after a rainstorm and see frogs believe it rained frogs."

During the period of extensive study of neurologic events temporally related to pertussis immunization, it became apparent to me and others that what was being called pertussis vaccine encephalopathy was not an encephalitis-like event, but instead was the first seizure or seizures of infantile epilepsy. From the period 1976 to 1994 five studies were done, all of which were controlled for temporally related events. It is clear from these studies that there is no such entity as pertussis vaccine encephalopathy. This led me to write a commentary published in 1990 entitled "Pertussis Vaccine Encephalopathy—It Is Time to Recognize It as the Myth That It Is." Studies of the period show that immunization with whole-cell pertussis vaccines called attention to the early signs of infantile epilepsy and perhaps moved the events forward in time, but did not cause these illnesses.

In regard to SIDS, the age of peak occurrence is at about 10 weeks of age, and since the first dose of DTP in the United States was administered at 2 months of age, the temporal association with immunization and SIDS would be expected. However, in the late 1970s and 1980s there was considerable coverage in the media of the possibility of a cause-and-effect relationship. However, a number of well-controlled studies failed to show a causal relationship between DTP immunization and SIDS. In fact, immunized children tended to have less SIDS than unimmunized children.

B. pertussis Produces Several Toxins and Other Important Antigens

Although dermonecrotic toxin (DNT) was identified by Bordet and Gengou in 1909, it was not characterized until 1963. Pertussis toxin (PT) was identified in 1948 but was not purified until 1962. Similarly, filamentous hemagglutin (FHA) was identified in 1947, lipopolysaccharide (LPS) in 1960, adenylate cyclase toxin (ACT) in 1973, tracheal cytoxin in 1982, and pertactin (PRN) in 1982.

From our studies of whole-cell pertussis vaccines, we concluded that the fever, local reactions, irritability, and persistent crying are due to LPS. Increased serum insulin following immunization appears to be due to PT. Although the cause of hypotonic-hyporesponsive reactions is not known, it may be due to hypoglycemia from PT-associated increased serum insulin.

Acellular Pertussis Vaccines

The first acellular pertussis containing vaccines (DTaP vaccines) were developed and put into use in Japan. Using centrifugation techniques, Yuji Sato, Department of Bacteriology, National Institute of Health, Tokyo, Japan, and colleagues concentrated supernatant fluid from cultures of *B. pertussis* that contained PT and other antigens, including LPS. The layers containing LPS were separated by ultracentrifugation and discarded, while PT was inactivated with formalin. These vaccines, produced by six different manufacturers, were put into general use in Japan in 1981 and were shown to be effective. However, because immunization was

not carried out by conventional schedules, and the studies of reactogenicity and efficacy were less than adequate, further studies were necessary prior to the licensure of DTaP vaccines in the United States and western Europe. A number of different types of vaccines were evaluated in studies in Europe and Africa in the early 1990s.

These vaccines included a single PT component vaccine, two-component vaccines with PT and FHA, three-component vaccines with PT, FHA, and PRN, and four-component vaccines with PT, FHA, PRN, and fimbriae. One of these latter vaccines, which is presently in use in the Untied States, is called a five-component vaccine because it contains both serotypes of fimbriae. Studies in the mid-1990s showed that the vaccines that contained PRN were more efficacious than vaccines containing PT or PT-FHA.

In 1991 the first DTaP vaccine was approved for the fourth and fifth doses in the United States. Subsequently, in 1996 and shortly thereafter, a number of vaccines were approved for the primary series (doses one, two, and three). With two exceptions, DTaP vaccines are less efficacious than DTP vaccines.

Most recently we have had the licensing of two tetanus, diphtheria, and acellular pertussis vaccines (Tdap vaccines) for adolescents and adults. Both of these vaccines have components similar to their pediatric counterparts but they contain less diphtheria and smaller amounts of some or all of the pertussis antigens. The antibody responses to these vaccines in adolescents and adults are significantly greater than the responses in children after three doses of the pediatric vaccines. This difference suggests that these vaccines will be highly efficacious and should protect recipients for more than 5 years.

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