The role of the acellular pertussis vaccine and the demise of 'Pertussis Pete'

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Pertussis or whooping cough is an acute infectious disease of the respiratory tract caused principally by *Bordetella pertussis* and less commonly by *Bordetella parapertussis* (1). Until two decades ago, pertussis in adults was a medical curiosity (2-4), but with the purification of specific *Bordetella* species antigens, the development of reliable enzyme immunoassays allowing accurate serological diagnosis and better understanding of the duration of immunity from vaccination, it has been clearly demonstrated that *B pertussis* is a common cause of prolonged cough in adults. Indeed, its incidence has been increasing gradually over the past decade in both adults and adolescents. Given the recognition of the importance of pertussis as a cause of prolonged cough in adults and the advent of the new acellular pertussis vaccines, it is timely to review current concepts of the pathogenesis of pertussis, its epidemiology in adults and the utility of the anticipated impact of the acellular vaccine.

The roots of the name pertussis ('per' meaning intensive or pernicious and 'tussis' meaning cough) aptly describe the clinical manifestations of this disease, characterized by progressive, repetitive paroxysmal coughing with relatively minor systemic complaints. The term 'whooping cough' comes from the characteristic, inspiratory whoop noted frequently in children. The disease was first mentioned in England in the 16th century, but the illness was first described clearly by Sydenham in the 17th century (5). It was not until 1906 that the etiological agent from the respiratory tract of affected children was isolated by Bordet and Gengou (6).

B pertussis and *B parapertussis* are nonmotile, Gram-negative coccobacilli, which are among the smallest of bacteria, measuring less than 1 µm in width and length. In recent

years, a great deal of information has been generated on the virulence factors produced by *B pertussis*, the regulation of their expression and their molecular mechanisms of action. The virulence factors of *B pertussis* have been recently reviewed (7), and only a brief description will be provided. Important virulence factors include adhesins, adenylate cyclase (AC) toxin, tracheal cytotoxin (TCT) and pertussis toxin (PT). Adhesins or agglutinogens (including filamentous hemagglutinin [FHA], pertactin and fimbriae), and possibly TCT and PT, provide a redundant series of interactions with ciliated respiratory epithelial cells beginning in the nasopharynx and descending into the deeper regions of the tracheobronchial tree (8). FHA appears to mediate the binding of *B pertussis* to multiple cell types via interaction with specific integrins within the cell surface, and is a component of most acellular vaccines. Pertactin is an outer membrane protein that contributes to binding and has been included in the new acellular vaccines. Fimbriae are also involved in binding to the cell surface but in a later stage of the process. With the redundancy of the adhesins that attach to the cell surface and with contributions by PT and TCT to the binding process, it has been difficult to determine precisely the sequence of events and the relative role played by each of the factors in the infective process.

Following the expression of the adhesion factors, the timed and regulated production of protein exotoxins and TCT are believed to be the molecular basis for the clinical manifestations of pertussis (9). The production of AC toxin, TCT and PT have profound effects on the host, and the latter is proposed to be the major factor responsible for the characteristic clinical picture of pertussis. The AC of *B pertussis* is also a hemolysin and has the ability to catalyze the production of

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very high levels of cyclic AMP, which has a profound effect on the antibacterial functions of phagocytes. This toxin also induces apoptosis in macrophages and other cells. The molecular structure of TCT, which is a degradation product of the recycling process of the peptidoglycan layer, has been determined (10), and has the ability to cause stasis of cilia and lethal effects on the respiratory epithelial cells. At the molecular level, TCT induces interleukin-1 production and nitric oxide synthase. PT is a member of a group of bacterial ribosyl transferases that have the ability to modify specific host proteins, particularly host cell G proteins through the inhibition of signal transduction. Because of its action on several target cells, it causes a variety of effects (7). Intratracheal administration of pure *Bordetella* species organisms and PT-deficient *Bordetella* species organisms in a rat model points to PT having a role in the induction of the cough in pertussis (11,12). The prolonged duration of the cough supports the concept of involvement of a long acting toxin. PT has other biological effects, including induction of lymphocytosis, sensitization to the effects of histamine and enhancement of glucose utilization. Whether PT acts alone in its pathogenic role, or whether it requires other factors or promoters, has not been completely elucidated. PT is included as a component of all acellular pertussis vaccines.

Pertussis is a disease with worldwide distribution. Much of the knowledge of its epidemiology and natural history was obtained in the early part of the 1900s, before the first vaccine was introduced in the late 1940s. It occurs throughout the year, and the attack rate is governed largely by the intimacy and frequency of exposure to susceptible individuals. Intrafamilial attack rates for susceptible individuals were often reported to be as high as 70% to 80%, in keeping with this being a very contagious agent. The disease was not only endemic but also had epidemic peaks every two to five years. In the prevaccine era, average attack rates in the United States were reported to be 157/100,000 population. However, with reporting estimated at only 18%, the adjusted attack rate was considerably higher at 872/100,000 population. Between 60% to 80% of the cases were reported in children younger than five years of age, and fewer than 3% of cases occurred in persons 15 years of age or older (5). Pertussis was an important cause of infant mortality, with death rates peaking at 4.3/1000 population at one time. Pertussis in the adult population in the prevaccine era was considered to be uncommon and often was less severe in its symptomatology. This can likely be attributed to repeated exposures to pertussis as a child and adolescent, leading to high adult immunity. However, the importance of adults as reservoirs of *Bordetella* species was emphasized in several publications, and Cherry (5) presented an excerpted vignette from Luttinger's original 1916 description of 'Pertussis Pete'. Over several weeks of staying with various relatives, he spread pertussis to several children before setting sail for Italy, having enlisted in the army.

In the postvaccine era, the incidence of pertussis was dramatically reduced, but it remained at a low level of endemicity with continued cycling epidemic periods. This observation

suggested that immunization controlled the disease but not necessarily the circulation of the organism in the population. The postvaccine era has also seen a shift in the peak age of disease compared with the prevaccine era. In the United States from 1982 to 1997, the pertussis attack rate demonstrated a modest increase, and a significant contribution was considered to be the result of an actual increase of pertussis in adults or at least increased recognition in this population (13). A recent study of an outbreak of pertussis in Vermont, United States revealed that 23% of cases were found in those 20 years of age or older (14). The reported incidence of pertussis in adolescents in Massachusetts, United States rose from 13/100,000 population in 1989 to 121/100,000 population in 1996; it also rose in adults from 0.4/100,000 population to 6/100,000 population during the same time period (14). Data from the Centers for Disease Control and Prevention revealed that the proportion of all reported cases that occurred in persons 10 years of age or older rose from 13% in 1980 to 47% in 1998 (14). Not all of these increases were considered to be related to improved recognition and reporting. In these and other reports on the occurrence of pertussis in adults (15-21), common features included paroxysms of coughing and a cough lasting for longer than two weeks. Thus, it is clear that adults probably represent the majority of patients with *B. pertussis* and the major reservoir of infection.

The incidence of pertussis in Canada also declined dramatically after the introduction of the whole cell vaccine but has been increasing in the past decade (22,23), despite high vaccine coverage in children younger than seven years of age. During the 1990s, the average annual incidence was 24/100,000 population for persons 10 to 19 years of age and 2.7/100,000 population for those 20 years of age or older. Three Canadian studies estimated that the secondary attack rate of pertussis in adolescents and adults by household contact ranged between 11% to 18% for those 18 to 29 years of age and 8% to 33% for those 30 years of age or older (24-26). It has recently been estimated that 10% to 25% of Canadian adolescents and adults are susceptible to pertussis (27). The explanation for these findings is waning immunity in those who had received the whole cell vaccine during childhood, a decline in the population that may have acquired natural infection with longer lasting immunity, improvements in diagnosis and surveillance, and possible genetic changes in current strains compared with the strains of *B. pertussis* from which the original whole cell vaccine was prepared.

The search for less reactogenic vaccines for infants and children led to the development of the acellular pertussis vaccines, which contain one or more purified proteins of the pertussis organism, including PT, FHA, pertactin and fimbrial agglutinogens. The safety and immunogenicity of these preparations were initially demonstrated in adults before their administration to infants and children (28-36). These studies paved the way for the use of acellular vaccines as a booster immunization for older children and adults. The Canadian National Advisory Committee on Immunization recently released recommendations for the adult use of an

acellular pertussis vaccine, which is combined with tetanus and diphtheria toxoids (27). These recommendations were made with the acknowledgement that there are little data on the effect of a booster dose of an acellular preparation of a pertussis vaccine on the epidemiology of pertussis. The combined tetanus-diphtheria-acellular pertussis vaccine, which is the first such product licensed in Canada, is currently recommended as the replacement for the usual tetanus-diphtheria booster dose used in previously immunized adults and adolescents 12 years of age and older. The vaccine is not recommended for a primary series. The goal is to reduce the morbidity and mortality associated with pertussis infection in Canada. An interesting debate is whether the new combined vaccine should be offered universally to adults at 10-year intervals with the potential to reduce the reservoir of adult carriage and transmission to infants and children, or whether selective targeted programs (day care workers, health care workers) would be more cost effective. As new data emerge, answers to these questions should become available to direct policy makers regarding the best options on a population basis. Regardless of the course of action taken, the increasing incidence of pertussis noted in the past two decades is less likely to continue, and hopefully there will be no new appearances in the medical literature of 'Pertussis Pete'.

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