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Acellular Pertussis Vaccine Safety and Efficacy in Children, Adolescents and Adults

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Abstract

This review offers a perspective on the acellular pertussis vaccine efficiency trials concluded in the 1990s and presents the main conclusions of a meta-analysis of 52 studies that assessed the safety and efficacy of the diphtheria-tetanus (DT)-whole cell pertussis (DTwP) and DT-acellular pertussis (DTaP) vaccines administered to children. A clear serological correlate of immunity to pertussis following DTaP vaccination was not identified despite an intensive analysis. It can be speculated that this may be because various combinations of antibody to agglutinogens (pertussis toxin, filamentous haemagglutinin, pertactin and fimbriae) provide protection, or because serum antibody levels and responses do not uniformly reflect mucosal IgA antibody levels.

Long-term efficacy following DTaP vaccination is becoming characterised and cell-mediated immunity (T-cell memory) may have importance. DTaP vaccination appears to establish herd immunity after sufficient uptake within communities and countries. As experience with DTaP vaccine safety has accumulated, a 1–2% occurrence of large, local injection reactions with all products has been defined for booster doses. The pathophysiological mechanisms for the reactions are not established but a majority appear likely to be IgE-mediated reactive oedema and a minority to be IgG-mediated reactive Arthus-type reactions. DTwP

and DTaP combinations with other vaccines have been studied and licensed; the most controversial combination products are the DTaP/*Haemophilus influenzae* type B polysaccharide conjugate vaccines.

Pertussis epidemiology is changing with a clear increase in occurrence in adolescents and adults. This development has spurred studies and licensure of safer DTaP vaccines for this older population. The economic impact of pertussis and transmission from adults to vulnerable infants provides a cost-benefit justification for widespread use of DTaP vaccines in all age groups with routine boosting every 10 years.

To conduct this review of acellular pertussis vaccine safety and efficacy in children, adolescents and adults the MEDLINE database was searched for papers involving pertussis illness, and pertussis vaccines for the time span 1998–2004. From these papers, those considered to be most important and relevant to the field were selected. Eight efficacy trials evaluating acellular pertussis vaccines were conducted in the early 1990s; the results were reported in publications from 1995 to 1998.[1-8] With the perspective of time and the opportunity to evaluate the merits of each trial, conclusions can be drawn regarding relative safety, immunogenicity and efficacy of pertussis products, which were subsequently licensed and are available for use. During the efficacy trials there was an effort to establish a correlate of immunity for pertussis vaccination so that future efficacy trials would not be necessary. Thus far, a clear correlate has not emerged, although several explanations have been offered. The most compelling in our view relates to the failure to assess mucosal immune responses, since *Bordetella pertussis* is a mucosal pathogen. The acellular pertussis vaccines have shown long-term efficacy but, when administered, booster immunisations have been associated with large local injection site reactions in 1–2% of patients. The mechanism of the reactions has been studied and is discussed in this review. Herd immunity can be established with acellular pertussis vaccination but sustained high levels of vaccination are necessary.

Diphtheria-tetanus (DT)-whole cell pertussis (DTwP) combination vaccines led the way to the development of DT-acellular pertussis (DTaP) combination vaccines. However, reduced immunogenicity to DTaP/*Haemophilus influenzae* type B (Hib) combination vaccines led to differing recommendations in various countries regarding their use. The resurgence of Hib disease in the UK after the introduction of a DTaP/Hib vaccine has been attributed to the reduced immunogenicity of the Hib component and a re-examination of reliance on immunological memory for protection against Hib disease.

The epidemiology of pertussis is changing. Adolescents and adults, acting as reservoirs, are contracting the disease and transmitting the organism to infants. These observations have led to the development of acellular pertussis vaccines combined with diphtheria and tetanus antigens in formulations suitable for use in adolescents and adults. Trials have shown these products to have excellent safety and immunogenicity characteristics. With a growing appreciation of the economic impact of pertussis strategies, regulatory agencies may begin to recommend the use of these safely used and effective vaccines in children, adolescents and adults.

1. Perspectives on the Acellular Pertussis Efficacy Trials

Eight efficacy trials evaluating nine different DTaP vaccines given in infancy were completed during the 1990s (table I).[1-8] The interpretation of the results and comparisons among the trials remains complex. The design of the trials differed, and only three were randomised, fully blinded, controlled, comparative studies. The WHO case definition of pertussis was not strictly applied in all trials. Some investigators argued that the WHO case definition eliminated some laboratory-confirmed cases

from efficacy calculations. Because these cases turned out to be more common in vaccinees than in controls, vaccine efficacy may have appeared better than it truly was, whereas less effective vaccines may have appeared comparable with their more effective counterparts.[9] Observer bias may have occurred in all the trials and it may have impacted on vaccine efficacy calculations.[9,10] That is, if vaccinated individuals presented with milder disease than control-vaccinated cases, then even in double-blind placebo-controlled trials the study nurses and evaluating physicians might have dismissed mild cases of pertussis. In contrast with the more severe presentations of the disease, the milder cases would not receive cultures or serology assessment. If this occurred, a less effective vaccine that prevented typical disease, but not mild disease, could have been evaluated as a more effective vaccine than it actually was, resulting in an over-estimation of efficacy. This probably occurred in all vaccine trials, but was even more of a problem with the case-control, non-randomised and household contact methodologies.

A meta-analysis of all trials conducted until 2002 to assess the efficacy and safety of whole-cell and

Table I. Results of efficacy trials of acellular pertussis vaccines conducted in the 1990s

Study location, year	Case definition[a]	Vaccine	Cases	WHO [% efficacy (95% CI)]
Randomised, fully blinded, controlled comparative studies				
Stockholm, 1992[1]	WHO	GSK two-component (not licensed)	159	59 (51, 66)
		Tripacel™	59	85 (81, 89)
		Connaught DTwP	148	48 (37, 58)
Italy, 1992[2]	WHO	Infanrix®	37	84 (76, 89)
		Acelluvax™	36	84 (76, 90)
		Connaught DTwP	141	36 (14, 52)
Stockholm, 1993[3] [b]	WHO	GSK two-component (not licensed)	Not applicable/ no data	No data
		Acelluvax™	21	RR 2.55 (1.55, 4.33)
		Daptacel®	13	RR 1.40 (0.78, 2.52)
		Wellcome DTwP	15	RR 1.00
Randomised, fully blinded, controlled noncomparative studies				
Gothenburg, 1991[4]	WHO	Certiva™	72	71 (63, 86)
Senegal, 1990[5]	Modified WHO	Triavac™	24	74 (51, 86)
		PMC-Fr-DTwP	7	92 (81, 97)
Non-randomised diphtheria comparator				
Erlangen, 1991[6]	Modified WHO	Acel-Imune®	≤45	85 (77, 91)
		Lederle DTwP	≤18	93 (88, 96)
Household contact				
Mainz, 1992[7]	WHO	Infanrix®	7	89 (77, 95)
		Behring DTwP	1	93 (83, 100)
Case control				
Munich, 1993[8]	Modified WHO	Tripedia®	4	96 (63, 99)
		Behring DTwP	1	96 (71, 100)

a Results are for a three-dose infant immunisation series; effects of any booster dose are not included. WHO efficacy results are based on the case definition closest to that of the WHO. Some of the WHO results were calculated from data provided in the referenced source; such results may represent crude, rather than adjusted, efficacies. WHO case definition: ≥21-day paroxysmal cough plus bacteriological, serological or epidemiological confirmation of *Bordetella pertussis*.

b Results are presented in relative risk instead of efficacy rates. No data are available for the GSK two-component vaccine as unblinding and boosting was necessary because of poor efficacy.

DTwP = diphtheria-tetanus-whole cell pertussis; **GSK** = GlaxoSmithKline; **PMC-Fr** = Pasteur Merieux Connaught-France; **RR** = relative risk.

acellular pertussis vaccines administered to children was published in 2003: 52 studies (49 randomised controlled trials, 3 cohort studies) were included.[11] The conclusions of this comprehensive analysis were as follows.

1. All tested whole-cell and acellular vaccines were significantly more effective than placebo against pertussis.

2. Using the WHO definition of pertussis infection, whole-cell vaccines showed higher efficacy than placebo against pertussis (pooled efficacy = 78%) but efficacy varied significantly between vaccines (efficacy for DTwP vaccines ranged from 46% to 92%).[1,2,6] The pooled absolute efficacy for acellular vaccines was 73%; efficacy was 67–70% for one- or two-component vaccines, 84% for three-component, 80% for four-component and 84% for five-component acellular vaccines.

3. Absolute efficacy against mild pertussis was 42% for two-component, 70–71% for three-component and 76% for five-component vaccines. Differences between vaccines with three to five components were not significant for either WHO-definition or mild pertussis.

4. The relative efficacy of acellular and whole-cell vaccines varied depending upon the case definition of pertussis used. Three- and five-component acellular vaccines were equally or more effective than whole-cell comparators against WHO-defined pertussis, while two- and four-compartment vaccines were less effective. Comparator whole-cell vaccines were more effective than two-component acellular vaccines, less effective than three-component acellular vaccines and as effective as five-component acellular vaccines against mild pertussis.

5. Regarding the safety of pertussis vaccines, whole-cell vaccines had a significantly higher incidence of swelling and indurations than DT or placebo vaccines. The incidence of temperature >38°C and of crying for >2 hours was significantly higher with the whole-cell vaccines than in the DT or placebo vaccines. The association between whole-cell vaccines and hypotonic-hyporesponse episodes or convulsions was not significant; however, this may be due to the infrequency of these events. Acellular pertussis vaccines did not cause a higher incidence of local signs, fever, convulsions, hypotonic-hyporesponse episodes or prolonged crying than DT or placebo vaccines.

6. Direct comparison of the safety of acellular and whole-cell pertussis vaccines showed that all types of acellular pertussis vaccines were associated with a lower incidence of local reactions and fewer incidences of fever than whole-cell comparators.

2. Search for a Correlate of Immunity

Unlike immunisation against other vaccine-preventable illnesses such as tetanus and diphtheria, in which a protective titre of antitoxin antibody has been determined, a serological correlate of immunity for acellular pertussis vaccines has not been established. Despite intensive effort, the clinical efficacy trials of the acellular pertussis vaccines did not yield a clear correlation between specific antibody titres and protection against pertussis infection. This issue continues to be the subject of ongoing investigation and data analysis. There are relationships between immunological responses and the protective activities of the acellular vaccines, but the precise quantities of antibody or measures of cell-mediated responses are yet to be fully understood.

Individual and various combinations of antibody titres have been evaluated as possible correlates of protection. During a vaccine efficacy trial in Germany, Cherry et al.[12] collected sera from vaccinees who received DTaP or DTwP after the third or fourth doses of vaccine or at comparable time periods in DT vaccine recipients. Additionally, they collected postvaccination sera from individuals in each vaccine group at 3-month intervals, from which antibody kinetic curves were constructed. This allowed an estimate of specific antibody values to pertussis toxin (PT), pertactin, filamentous haemagglutinin (FHA) and fimbriae-2 at times of household exposure to *B. pertussis* when they occurred. The imputed geometric mean antibody values to PT, pertactin and fimbriae-2 at the time of household exposures to *B. pertussis* infection were higher in non-cases than in cases. A multivariate analysis found that only pertactin and PT were sig-

nificant in protection. Individuals with imputed pertactin values of <7 ELISA Units (EU)/mL had a 67% chance of infection regardless of the PT value. If the pertactin value was ≥7 EU/mL and the PT value was ≥66 EU/mL then all of those individuals were non-cases. Regression analysis showed that high versus low pertactin values were associated with illness prevention following household exposure. The presence of antibodies to FHA did not appear to contribute to protection when antibody to pertactin, PT and fimbriae-2 were present. The data were interpreted to suggest that pertactin is the most important pertussis vaccine antigen in multicomponent vaccines and that FHA may not be necessary.

In another household contact DTaP vaccine efficacy trial, Storsaeter et al.[13] also showed that antibodies to pertactin play an important role in protection from *B. pertussis* infection. Four groups of patients were studied in this trial: a placebo group receiving a DT vaccine, a group receiving a two-component DTaP vaccine containing PT and FHA, a group receiving a five-component DTaP vaccine containing PT, FHA, fimbriae-2 and -3 and pertactin, and a group receiving a DTwP vaccine. The predicted attack rate for children with 'low' (<5EU) levels of antibodies to pertactin, fimbriae-2 and -3, and PT was 66% for typical pertussis (WHO definition) and 88% for any laboratory-confirmed pertussis infection with at least 1 day of cough. Efficacy against typical pertussis was >70% when anti-pertactin or anti-fimbriae-2 and -3 antibody levels were 'high' (>5EU); efficacy was 85% when antibodies to pertactin and fimbriae-2 and -3 were both 'high'. In contrast, efficacy was approximately 46% when only anti-PT was 'high'. A third study by Deen et al.[14] found that no patients with clinical pertussis seen within 14–28 days of exposure had an IgG antibody level to pertactin in acute phase sera of ≥50 EU/mL or an agglutinin titre >256.

There are other supportive data for the notion that the presence of anti-pertactin antibody correlates with protection. Anti-pertactin antibodies appear crucial for phagocytosis of *B. pertussis*.[15] Antibodies of the IgA class directed to pertactin enhance binding and agglutation of *B. pertussis*.[16] The studies by Cherry et al.,[12] Storsaeter et al.[13] and Deen et al.[14] are valuable, but they have known shortcomings and their conclusions are not universally accepted.[17,18]

Immunogenicity data collected during efficacy trials of pertussis vaccines in infants suggest that antibodies may not be the sole determinants of resistance to the illness. Cell-mediated immunity (CMI) can regulate the nature and intensity of antibody response (T-helper-2 [T_h2]-mediated) and lead to the production of appropriate cytokines (T_h1-mediated) that help the natural immunoeffectors (phagocytes) eliminate an infectious agent. Therefore, CMI has been studied in murine models of *B. pertussis* infection, and in children and adults recovering from an infection or following vaccination against *B. pertussis*.[19-21]

Mills et al.[22] described using a murine model of pertussis infection that evaluated the rate of *B. pertussis* clearance following respiratory challenge in immunised mice and in mice with targeted disruption of the interferon (IFN)-γ receptor, interleukin (IL)-4 or immunoglobin heavy-chain genes. They evaluated three DTwP and five DTaP vaccines used in different efficacy trials. Clearance of and protection from infection in the murine respiratory challenge model correlated with observed vaccine efficacy. An absolute requirement for B cells and antibody to achieve bacterial clearance was established. A role for T_h1 cells in immunity generated by infection or vaccination with DTwP vaccine was demonstrated. Results of passive immunisation experiments suggested that protection early after vaccination with DTaP vaccine was mediated by antibody against multiple antigens. Their findings suggested that the mechanism of immunity against *B. pertussis* involves humoral and cellular immune responses.

Initial studies defining T-cell responses to *B. pertussis* in humans were conducted on T-cell lines and clones from adults who had contracted pertussis in childhood and uncloned T cells from immunised adults.[23-27] Subsequently, Ausiello et al.[28] showed a T_h1 predominant cellular immune response in healthy adult peripheral blood mononuclear cells (PBMCs) after stimulation using PT, FHA and

pertactin as antigens. Ryan et al.[29] examined the PBMC responses to *B. pertussis* in children during acute infection or after recovery and compared these results with those seen in unexposed and unvaccinated children. PBMCs from acutely infected or convalescent children proliferated and secreted cytokines following antigen stimulation. The proliferating T cells produced IFNγ (T_h1) and produced small amounts or undetectable quantities of IL-5 (T_h2). In contrast, the PBMC responses seen in the children who had not been infected or vaccinated were weak or undetectable. These findings suggested that T_h1 cells may play a role in protective immunity following infection with *B. pertussis* in children.

B. pertussis-specific CMI has been detected in children 14 months to 6 years of age following the primary vaccination series. Zepp et al.[30] investigated the specific CMI responses to pertussis-related antigens in infants 3–24 months of age following vaccination with a three-component DTaP vaccine. Their results showed that the vaccine induced T_h1 cell responses specific for the vaccine components (PT, FHA and pertactin) and that response increased over the course of the primary vaccination series. In contrast with declining antibody geometric mean anti-tetanus titres, the T_h1 responses were stable from the postprimary to the prebooster period of 15–24 months of age. In a similar manner, Cassone et al.[31] studied the CMI and antibody responses to Infanrix® **1** or Acelluvax™ before and at 1 and 14 months after vaccination. A CMI response, assessed by proliferation of PBMCs, to at least one *B. pertussis* antigen at one or both postvaccination assays was detected in 46%, 55% and 83% of DTwP, Infanrix® and Acelluvax™ vaccine recipients, respectively. The postvaccination responses measured at 14 months had equal or higher intensity than that of the 1-month postvaccination responses. In contrast, antibody titres to pertussis antigen fell to low or undetectable levels 14 months after vaccination. Ausiello et al.,[32] examining the cytokine profile of the CMI responses in those infants, showed that the response was primarily the T_h1 cell type. Some production of T_h2 cell type cytokines was observed, most frequently in those children receiving Infanrix®, as compared with Acelluvax™ or DTwP. Finally, Ausiello et al.[33] looked at the CMI responses and antibody titres in 4- to 6-year-old children who had a primary vaccination with a DT vaccine only and were infected by pertussis and in recipients of a DTaP vaccine (Acelluvax™) who had not contracted pertussis without any booster vaccine. Children receiving DT vaccination with no history of pertussis infection made up a control group. The DTaP recipients had the highest CMI responses to the three *B. pertussis* antigens (PT, FHA and pertactin). CMI response to PT showed the greatest difference between the groups, with the DTaP group having the highest lymphoproliferative response. The cytokine profile was of the T_h1 cell type.

In our view, it should be emphasised that *B. pertussis* is a mucosal pathogen. There is no systemic invasion or bacteraemic phase in the illness. Data from 40–50 years ago indicated that individuals vaccinated with whole-cell pertussis vaccine with high serum antibody levels that caused *B. pertussis* to agglutinate were protected from disease.[34-36] We now know that the agglutinin response is a composite response to a number of agglutinogens of *B. pertussis*, including PT and FHA (weaker agglutinogens) and pertactin and fimbriae-2 and -3 (stronger agglutinogens).[37] Since *B. pertussis* is a mucosal pathogen, serum agglutinin antibodies most probably transudate to the mucosal surface of the tracheobronchial tree, causing agglutination of bacteria there and subsequent phagocytosis and killing. Therefore, it is plausible that antibodies to strong agglutinogens (pertactin and fimbriae-2 and -3) would more clearly correlate with protection and antibodies to weaker agglutinogens (PT and FHA) would less clearly correlate with protection. The interpretation of FHA antibody levels seems particularly problematic. First, we speculate that FHA antibodies participate in pertussis immunity but the correlation is unclear because FHA has many epitopes shared with other Gram-negative bacteria.

1 The use of trade names is for product identification purposes only and does not imply endorsement.

Therefore, some of the antibodies we measure for FHA may not be specific for *B. pertussis* FHA antigen, or may be of much lower avidity and reduced functionality. Secondly, the importance of PT in the pathological effect of pertussis infection is irrefutable. Circulating antibody to PT neutralises the toxin, which in turn provides substantial protection against severe disease. Thirdly, the information on CMI, particularly T_h1-mediated immunity, is confusing. *B. pertussis* is an extracellular pathogen and the current understanding of T_h1 immunity would suggest that it is an effector for cytotoxic T cells relevant to intracellular pathogens. Surely T-cell memory is longer lasting than B-cell memory? Therefore, it is likely that T cells are important but their precise role currently remains unclear.

Lastly, it is also possible that the more important immune response is at the mucosal level (IgA). Although serum antibody responses and titres may predict mucosal antibody levels, this is not always the case.[38] Therefore, the dissociation between serum antibody levels and pertussis protection in some patients may be due to or explained by our inability to measure and precisely quantitate mucosal immune responses to the organism.

3. Long-Term Efficacy and Herd Immunity

The duration of protection induced by the acellular pertussis vaccines is unknown. This is of major importance for designing vaccine schedules and determining the timing of booster doses. Four double-blind, placebo-controlled efficacy trials demonstrated that acellular pertussis vaccines induced high protection against pertussis for approximately 18 months after the initial primary vaccine series of three injections.[1-4] Sustained immunogenicity and efficacy has been studied in the efficacy trial participants ranging from 14 months to 6 years after the initial primary vaccine series (table II).

The Italian efficacy trial was a double-blind, placebo-controlled, randomised trial in which infants received one of two acellular pertussis vaccines, a DTwP vaccine or a DT vaccine at 2, 4 and 6 months of age.[2] The DTaP vaccines both contained three components (PT, FHA and pertactin): one was produced by GlaxoSmithKline (Infanrix®) and the other by Chiron Biocine (Acelluvax™). The DTaP vaccines differed in the method of PT detoxification: Infanrix® contained formalin and glutaraldehyde detoxified PT, and Acelluvax™ contained a genetically detoxified PT. Efficacy against WHO-defined pertussis disease was 84% for both vaccines (Infanrix® 95% CI 76, 89; Acelluvax™ 95% CI 76, 90) over an average of 17 months' follow-up.[2]

In follow-up, Cassone et al.[31] evaluated cell-mediated and antibody responses to *B. pertussis* in a subset of children who had participated in the Italian efficacy trial. Samples were obtained at 1 and 14 months following the third vaccine at 6 months of age. A CMI-positive response to at least one *B. pertussis* antigen at either one or both of the postvaccination evaluations was detected in 46%, 55% and 83% of DTwP, Infanrix® and Acelluvax™ recipients, respectively. The CMI responses measured at 14 months equalled, or had increased frequency or intensity to, those measured at 1 month. Elevated antibody titres directed against the three antigens were present in all DTaP vaccine recipients 1 month after vaccination. The antibody titres fell to near undetectable levels 14 months after vaccination. In a larger subset of children participating in the Italian efficacy trial, Giuliano et al.[45] also showed a rapid decline of antibody titres to PT, FHA and pertactin to nearly undetectable levels 15 months after the third vaccine.

The Italian efficacy trial monitored the incidence of pertussis in each study group for two follow-up periods. The results of the initial trial reported on the first stage of follow-up, which ended when the average age of children was 24 months old.[2] An additional 9 months of observation ended when the average age of the children was 33 months old. During that time, the absolute efficacy was 78% (95% CI 62, 87) for Infanrix® and 89% (95% CI 79, 94) for Acelluvax™. Combining the initial and follow-up periods, the overall vaccine efficacy through an average of 33 months was >80% for Infanrix® and >85% for Acelluvax™.[40]

Table II. Long-term immunology and clinical efficacy data from the efficacy trials of acellular pertussis vaccines conducted in the 1990s

Trial/vaccine	Years since initial vaccine series as an infant				
	2	3	4	5	6
Stockholm trial[1]					
Tripacel™			Clinical efficacy sustained (2–6 years after vaccination)[39]		
Italian trial[2]					
Infanrix®	PT, FHA, PRN antibodies detectable and CMI responses to PT, FHA, PRN detectable (14–15 months after vaccination)[31]	Clinical efficacy sustained (33 months after vaccination)[40]		Clinical efficacy sustained (4–6 years after vaccination)[41]	
Acelluvax™	PT, FHA, PRN antibodies detectable and CMI responses to PT, FHA, PRN detectable (14–15 months after vaccination)[31]	Clinical efficacy sustained (33 months after vaccination)[40]		Clinical efficacy sustained (4–6 years after vaccination)[41]	
Goteburg trial[4]					
Certiva™	Clinical efficacy sustained (2 years after vaccination)[42]				
Erlangen trial[6]					
Acel-Immune®					Clinical efficacy sustained (6 years after vaccination)[43]
Munich trial[8]					
Tripedia®				Clinical efficacy stained (5–7 years after booster vaccination)[44]	

CMI = cell-mediated immunity; **FHA** = filamentous hemagglutinin; **PRN** = pertactin; **PT** = pertussis toxin.

Salmaso et al.[41] conducted an unblinded, prospective, longitudinal study of those children in the Italian efficacy trial who completed the second stage of follow-up and remained under active surveillance. The objective of the study was to estimate the persistence of protection from 3 to 6 years of age of both studied three-component DTaP vaccines. A total of 391 laboratory-confirmed infections were identified in the 3-year follow-up period. The mean duration of cough and spasmodic cough was shorter in the DTaP recipients than in the diphtheria recipients. Similar to the initial follow-up period, efficacy varied depending upon the severity of *B. pertussis* illness. Using the primary case definition of laboratory-confirmed *B. pertussis* infection and ≥14 days of spasmodic cough or ≥21 days of any cough, the efficacy was 78% (95% CI 71, 83) for Infanrix® and 81% (95% CI 74, 85) for Acelluvax™. When using a milder clinical presentation (any cough ≥7 days), the vaccine efficacies were 86% (95% CI 69, 81) for Infanrix® and 78% (95% CI 72, 83) for Acelluvax™.

The Swedish efficacy trial, like the Italian trial, was a double-blind placebo-controlled trial that evaluated the clinical efficacy of two acellular pertussis vaccines as compared with a DTwP and DT vaccine. A two-component DTaP containing PT and FHA (produced by GlaxoSmithKline and not licensed) and the five-component DTaP vaccine containing PT, FHA, pertactin and fimbriae-2 and -3, produced by Aventis Pasteur (Tripacel™), were studied. After three doses, the efficacy of the vaccines using a case definition of laboratory-confirmed pertussis or contact with an infected household member with paroxysmal cough for ≥21 days was 59% (95% CI 51, 66) for the two-component

vaccine and 85% (95% CI 81, 89) for Tripacel™ during a follow-up period of 2 years.[1]

Olin et al.[39] later described long-term follow-up efficacy data on the two DTaP vaccines from the Swedish trial. The study participants were between 3 and 7 years of age during the follow-up period of October 1997 to September 2000. Children who received three doses of the two-component DTaP vaccine (GlaxoSmithKline) had an incidence rate of pertussis of 88 per 100 000 person-years, which was higher than those children who had received the five-component DTaP vaccine Tripacel™, where the incidence rate was 66 per 100 000 person-years.

In their double-blind efficacy trial of mono-component pertussis toxoid vaccine, Certiva™, Trollfors et al.[4] vaccinated 3450 infants with DT with or without PT at 3, 5 and 12 months of age. Efficacy against pertussis, as defined by the WHO, was 71% from 30 days after the third vaccination, with an average follow-up of 17.5 months, and 75% in household contacts. Subsequently, Taranger et al.[42] reported longer-term efficacy data from this trial for an average follow-up of 2 years. The efficacy during the open follow-up period was 77% based on WHO-defined definition of pertussis in those children receiving PT vaccines. Efficacy against household exposure during this extended follow-up period was 76%. The investigators concluded that PT vaccine induced significant protection against pertussis for at least 2 years after the third injection.

Tripedia®, a two-component (PT and FHA) acellular pertussis vaccine manufactured by Aventis Pasteur, was evaluated in a case-control efficacy trial in Munich, Germany from 1993 to 1995.[8] Infants were vaccinated with either Tripedia®, a DTwP vaccine, a DT vaccine or no vaccine at 2, 4 and 6 months of age. Protective efficacy after three doses of Tripedia® was 82% (95% CI 68, 90) for any cough ≥21 days' duration and 96% (95% CI 78, 99) for paroxysmal cough of ≥21 days' duration. Long-term efficacy for this vaccine was evaluated up to 5–7 years after a booster dose that was given at 18–24 months of age.[44] Tripedia® maintained an unchanged and high efficacy at 5–7 years after the booster dose. The efficacy varied according to the severity of the pertussis disease between 78% for any cough >7 days' duration and 97% for paroxysmal cough of ≥21 days' duration. These results were similar to the DTwP vaccine efficacy for typical pertussis.

A randomised, double-blinded efficacy trial evaluating a four-component acellular pertussis vaccine, containing PT, FHA, pertactin and fimbrae-2 (Acel-Imune®) was conduced in Erlangen, Germany from May 1991 to January 1992.[6] Two- to four-month-old infants received four doses of either DTaP or DTwP vaccine at 3, 4.5, 6 and 15–18 months of age. The efficacy of the vaccines varied depending upon the severity of the pertussis disease. When considering severe disease with ≥21 days of cough with paroxysms, vaccine efficacy was 85% (95% CI 77, 91) and 93% (95% CI 88, 96) for DTaP and DTwP vaccines, respectively. Both vaccines were less efficacious against milder disease, as defined by ≥7 days of cough: 72% (95% CI 62, 79) and 83% (95% CI 76, 88) for DTaP and DTwP, respectively. For DTaP vaccine, efficacy was higher after the fourth dose compared with after the third dose (76% vs 62% for cough ≥7 days' duration and 85% vs 78% for cough ≥21 days' duration with paroxysms).

The long-term effectiveness of Acel-Imune®, was reported by Lugauer et al.[43] A subset of the original study population participating in the Erlangen efficacy trial agreed to further prospective follow-up of ≥14 days of cough illness. Calculated efficacy for the 6-year follow-up period based upon physician-diagnosed pertussis was 89% (95% CI 79, 94) for DTaP and 92% (95% CI 84, 96) for DTwP. There was no evidence of decreasing efficacy over the time monitored.

Long-term immunogenicity and efficacy data are available for other DTaP vaccines given singly or within combination vaccines. Okada et al.[46] reported on the long-term persistence of serum antibody titres to vaccine antigens in children vaccinated with a DTwP vaccine, a five-component DTaP vaccine (Takeda) or a mixed schedule, given as three doses between 2 and 3 years of age and a booster dose at 4–5 years of age. Five to 7 years after the booster, antibody titres to PT and FHA were equivalent

among those children receiving four doses of DTwP, three doses of DTwP and one dose of DTaP, and four doses of DTaP. Meyer et al.[47] described long-term CMI responses in children 1–3 years after receiving a DTaP-based combination vaccine, although CMI responses were higher in children 1–3 years after receiving a DTwP-based combination vaccine. Esposito et al.[48] reported on the pertussis-specific humoral and cellular immunity in children 5 years after primary vaccination with a combined three-component DTaP and hepatitis B vaccine (DTaP-HBV; Infanrix®HepB). After 5 years, only a small number of vaccinated children had significant concentrations of IgG in serum against any of the three *B. pertussis* antigens; T-cell responses persisted in a minority of patients. Long-term follow-up immunogenicity data for a two-component DTaP vaccine (Tripedia®, containing PT and FHA) contained within a pentavalent combination vaccine (Pentavac®; Aventis Pasteur) was obtained 4.5 years after an initial vaccination series comparing a three- and a four-dose regimen given at 2, 4, 6 and 13 months or 3, 5 and 12 months of age.[49] There were no significant differences between the two groups with respect to antibodies against pertussis antigens. Only 44% of children had detectable PT antibodies. Ninety-four percent had detectable antibodies against FHA.[49]

Vaccine-induced herd immunity is an important aspect of sustained protection against a number of diseases, including pertussis. A combination of protection by vaccines and decreased circulation of pertussis is likely to be of importance for prevention of disease. Taranger et al.[50] provided solid evidence that transmission of pertussis in the Gothenburg, Sweden, population was interrupted by vaccination of children with a monocomponent PT vaccine. A significant decrease was observed in pertussis isolates and hospitalisations in vaccinated children, unvaccinated infants <6 months old and unvaccinated adults.

A contrasting result with that in Gothenburg occurred in Canada, where a cohort effect of lost herd immunity followed sustained use of a poorly protective DTwP vaccine.[51] Beginning in 1990, Canada experienced a resurgence of pertussis. The mean annual incidence increased 10-fold from 1990 to 1998 and the median age of cases shifted from 4.4 to 7.8 years. Pertussis occurred predominately in a cohort of children who were DTwP vaccinated from 1988 to 1998. Spread of pertussis occurred in all age groups. The introduction of a more efficacious DTaP vaccine restored protection from pertussis and re-established the herd effect.

The long-term follow-up studies discussed in this section demonstrate continued high efficacy rates despite low-sustained titres of antibodies directed towards pertussis antigens. Detection of the T_h1 type cells appears possible for a longer time frame than antibodies following vaccination. However, since *B. pertussis* is a mucosal, extracellular pathogen, the role of CMI in disease protection is unknown and controversial. Herd immunity plays a role in protection. With mucosal pathogens, repetitive infections can occur even with the same serotype of an organism, for example *B. pertussis*, *Mycoplasma pneumoniae* and *Helicobacter pylori*. The mucosal immune response is characterised by shorter duration and less durable memory. Perhaps this is why natural pertussis infection appears to be followed by susceptibility to reinfection within 2–5 years. In contrast, in vaccination-induced immunity the antigen is delivered parenterally and a systemic immune response is followed by sustained memory and durable protection for approximately 10 years.

4. Large Injection Site Reaction to Diphtheria-Tetanus (DT)-Acellular Pertussis (DTaP) Vaccination

Large injection site local reactions including extensive limb swelling have been reported after vaccination with DTaP products,[36,52-63] as well as other vaccines.[64-67] Extensive limb swelling may involve an entire extremity (from hip to foot or shoulder to hand) or, more commonly, swelling of the proximal injection site area (hip to knee or shoulder to elbow). The US FDA recently reviewed data from the US Vaccine Adverse Event Reporting System (VAERS) to: (i) characterise reported cases of extensive limb swelling; (ii) identify the vaccine in-

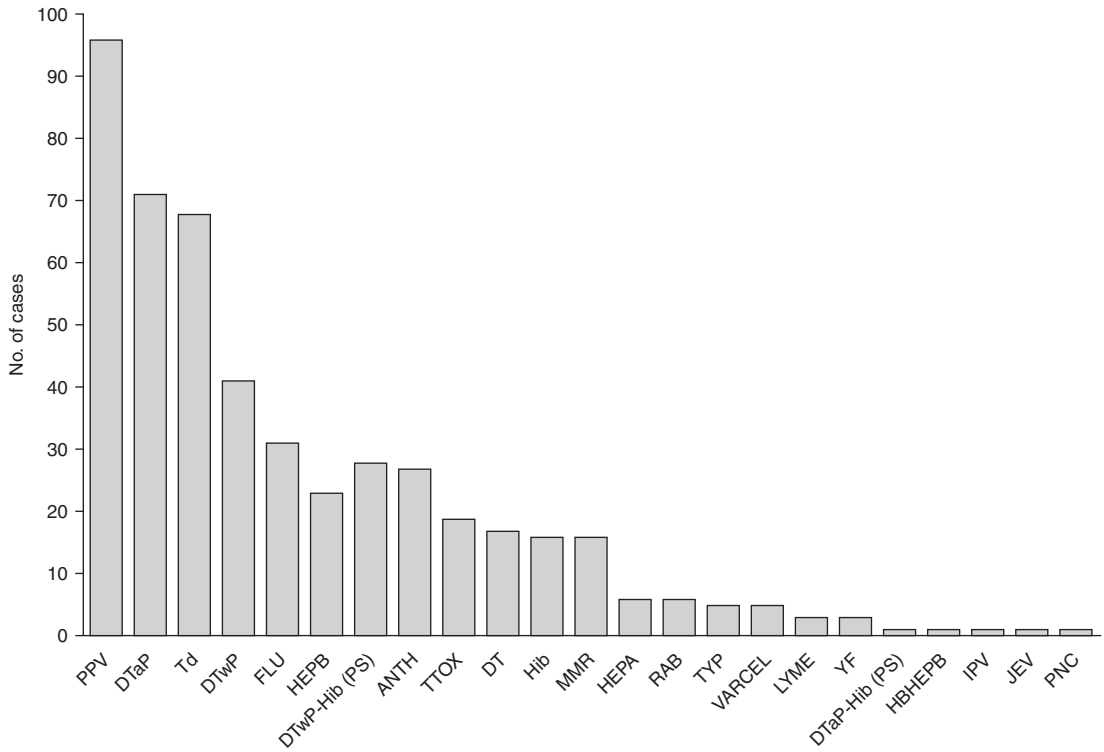

Fig. 1. Number of cases of large local reactions to 23 different vaccines. Distribution of cases of extensive limb swelling after administration of a single vaccine, by vaccine type, in reports to the Vaccine Adverse Event Reporting System, 1 July 1990 through 16 January 2003 (n = 418). **ANTH** = anthrax vaccine; **DTaP** = diphtheria-tetanus-acellular pertussis vaccine; **DTwP** = diphtheria-tetanus-whole cell pertussis; **DTwP-Hib (PS)** = diphtheria and tetanus toxoids, acellular pertussis vaccine, and Hib (adsorbed paediatric); **FLU** = influenza virus vaccine; **HBHEPB** = Hib and HEPB; **HEPA** = hepatitis A vaccine; **HEPB** = hepatitis B vaccine; **Hib** = *Haemophilus influenzae* type B vaccine; **IPV** = inactivated polio virus vaccine; **JEV** = Japanese encephalitis virus vaccine (inactivated); **LYME** = Lyme disease vaccine; **MMR** = measles, mumps and rubella virus vaccine (live); **PNC** = pneumococcal 7-valent conjugate vaccine; **PPV** = polyvalent pneumococcal vaccine; **PS** = polysaccharide; **RAB** = rabies vaccine; **Td** = tetanus and diphtheria toxoids (adsorbed adult); **TTOX** = tetanus toxoid; **TYP** = typhoid vaccine; **VARCEL** = varicella vaccine (live); **YF** = yellow fever vaccine.

volved; (iii) describe concomitant inflammatory responses; and (iv) examine the role of dose numbers.[67]

Although much attention has been given to large local reactions following DTaP vaccination, the VAERS database disclosed that 23 different vaccines caused extensive limb swelling; the most common of which was polyvalent pneumococcal vaccine (figure 1).[67] DTaP, tetanus and diphtheria toxoids (adsorbed adult DT), DTwP and influenza vaccines completed the list of the top five vaccines causing these types of reactions. Among vaccinees ≤7 years old, extension limb swelling was more likely with the fourth and fifth doses of DTaP (and DTwP vaccines) than after the primary doses. Specifically, in the VAERS, when limb swelling was reported it occurred more commonly after the fourth (33% of all reports) and fifth DTaP dose (31%) than with the first (10%), second (12%) and third dose (3%), with 10% of reports missing data on the dose number. Injection site reactions generally followed the same pattern as limb swelling in terms of more common occurrences after the fourth (48% of all reports) and fifth dose (20%) compared with the first (7%), second (3%) and third (6%) DTaP doses. Interestingly, for other vaccines for which more than one dose is generally recommended, including polyvalent pneumococcal vaccine, DT, influenza vac-

cine, hepatitis B vaccine, DTwP, and DTwP-Hib combination vaccines, neither extensive limb swelling nor other injection site reactions were reported more frequently with increasing dose number. However, dose numbers were missing from many of the reports involving these vaccines.

The pathophysiological mechanism(s) to explain large local reactions and extensive limb swelling following DTaP vaccination has been an area of controversy. Some investigators have suggested that these reactions are antibody-mediated Arthus-type reactions and/or that prior sensitisation to antigens or excipients in the vaccines are caused;[36,56,59-61,63] however, there is no consensus.[64,68,69] Rennels et al.[60] found a significant association between limb swelling after DTaP vaccination after dose four and diphtheria toxoid content, and of large local reactions after dose four or five and pertussis toxoid or aluminum content. No relationship could be established in this study between levels of serum antibody to diphtheria or pertussis toxoid and rates of swelling, as would be expected for antibody mediated Arthus-type reactions. However, Liese et al.[61] did find such an association. The relationship between the quantity of aluminum in DTaP vaccines and rates of extensive swelling reactions was later found to be inconsistent.[63] Both pertussis disease and pertussis vaccines have been shown to enhance the development of IgE-specific anti-PT antibody.[70] Aluminum adjuvants increase levels of antigen-specific IgE and promote T_h2-type responses,[71] and it has been shown that vaccines containing aluminum adjuvant induce higher IgE antibody levels to PT and cause more local reactions than non-aluminum-containing vaccines.[72] However, Edelman et al.[73] could not establish a relationship between large local reactions and IgE antibodies to PT after DTaP vaccination. Using skin tests with vaccine antigens, Schiefele et al.[74] suggested that CMI responses may account for some large local and limb swelling reactions. Thus, the cause of extensive limb swelling and many of the large local reactions following DTaP vaccination is currently unclear and most probably is multifactorial, representing a combination of host and immunological factors.

There are two general patterns to the large local and limb-swelling reactions following DTaP. In some patients the reaction has an onset in the first 24 hours following vaccination, typically without associated pain or reduction in limb movement, without local redness and without systemic symptoms such as fever. In summary, the reaction resembles a benign reactive oedema,[58] suggesting local changes in vascular permeability.[75] A second type of reaction has an onset at 24–72 hours after vaccination, typically with associated discomfort or pain, reduced limb movement and local redness, but without systemic symptoms such as fever. In summary, the reaction suggests an important role for inflammatory mediators and resembles an Arthus-type reaction. Generally, when extensive limb swelling or large injection site reactions occur following DTaP vaccination, about two-thirds take the pattern of benign reactive oedema and one-third take the Arthus-type pattern. There is no evidence that extensive limb swelling following a fourth DTaP dose will be followed by a similar reaction to a fifth dose.[60] The reaction subsides spontaneously without sequelae.[60]

Extensive limb swelling and large local reactions following DTaP vaccination are uncommon. A retrospective study of the safety of DTaP vaccines in Japan found extensive limb swelling in 2 per 100 000 vaccinees after a third or fourth dose.[52] In the multicentre acellular pertussis trials sponsored by the US National Institutes of Health (NIH) evaluating the fourth sequential dose of a DTaP vaccine, injection site swelling >50mm occurred in about 4% of vaccinees;[36] following the fifth sequential dose at a patient age of 4–6 years, swelling >50mm occurred in about 12% of vaccinees.[59] When data from these NIH trials were reviewed for unsolicited reports of extensive limb swelling, 20 (2%) of 1015 children who received four sequential DTaP doses experienced this reaction as did 4 (2.7%) of 146 vaccinees who received five sequential DTaP doses.[60] More recently, a retrospective population-based assessment of medically attended injection

site reactions following DTaP vaccination was completed in the US.[62] During the 4-year study period, 76 133 doses of DTaP were administered and 26 (0.03%) medically attended injection site reactions were identified; of the 26, 6 followed the fourth dose and 18 followed the fifth dose; rates of approximately 1 per 3000 and 1 per 1000 vaccinations, respectively. Characteristics of the 24 medically attended injection site reactions after DTaP vaccination given as the fourth or fifth dose in the US pertussis vaccination series is shown in table III. Large local injection site reactions and limb swelling are very infrequent adverse events following acellular pertussis vaccination of adolescents and adults. Van der Wielen et al.[76] described injection site reactions (>50mm) in 5.2% of 96 DTaP-vaccinated adults, 5.1% of 98 DT-vaccinated adults and 1.0% of 96 acellular pertussis-vaccinated adults. Schmitt et al.,[77] Halperin et al.,[78] Rothstein et al.[79] and Edwards et al.[80] did not describe any large local reactions or extensive limb swelling in the acellular pertussis vaccine evaluations in adults.

Table III. Characteristics of 24 medically attended injection site reactions after diphtheria-acellular pertussis (DTaP) vaccination given as the fourth or fifth dose in the pertussis vaccination series[60]

Characteristic	No. of reactions
Vaccination site	
Thigh	8
Upper arm	16
Onset after vaccination	
Same day	4
1 day	9
2 days	3
Not reported	8[a]
Reported reaction size	
2–5cm	6
≥6cm	10
Not reported	8
Associated signs and symptoms	
Redness	23
Swelling	16
Pain or tenderness	10
Pruritus	4

a Although the date of onset of the reaction was not reported in the medical record, the evaluation visit was within 3 days of vaccination for seven of the eight patients and was on day 6 post-vaccination for one patient.

5. DT-Whole Cell Pertussis (DTwP) and DTaP Combination Vaccines

The number of recommended vaccines that require injections has increased substantially over the last 17 years. The US schedule for active immunisation of healthy infants and children in 1986 involved a single vaccine injection at each of the scheduled well child visits, according to the American Academy of Pediatrics' *Red Book*. The 2003 recommended schedule involves three to five injections at most well child visits.[81] Combination vaccines offer the following benefits: (i) decreased number of injections; (ii) decreased number of visits; (iii) tangible public health benefits; (iv) decreased cost of administration; (v) increased compliance; (vi) ease of storage; and (vii) improved record keeping and tracking of vaccine administration. Thus, the demand for combination vaccines is increasing and many combination vaccines containing acellular pertussis components are in development.

5.1 Pertussis Vaccine Combination Products

5.1.1 DTwP-Haemophilus influenzae Type B (Hib)-Polysaccharide (PS) Conjugate Vaccines

DTwP vaccines from several manufacturers have been combined with the four available Hib-polysaccharide (PS) conjugate vaccines (PRP-CRM197 [Wyeth], PRP-OMP [Merck] and PRP-T [Pasteur Merieux Connaught and GlaxoSmithKline]) [see previous publications[82-99] for more information]. The reactions produced by the combination products have been similar to those observed with separate vaccination; virtually all of the local and systemic adverse effects are attributable to DTwP. Antibody levels to the antigens contained in these combination vaccines have been typically unaffected or decreased modestly, depending on the product and the study population.[100] Similar to observations when DTwP was mixed with plain Hib-PS,[101,102] Hib-PS antibody responses were lower compared with separate and simultaneous DTwP and Hib-PS administration in nearly all of the studies. Antibody levels to

pertussis antigens have been reported to be reduced with the DTwP-Hib conjugate vaccine combination in some, but not all, studies.

5.1.2 DTaP-Hib-PS Conjugate Vaccines

DTaP-Hib-PS conjugate combination vaccines were first studied as boosters in children primed with DTwP[100,103] and DTaP.[104,105] Three major vaccine companies following similar protocols, using DTaP and Hib-PS conjugate products as combinations compared with separate, simultaneous injections at 2, 4 and 6 months of age, found the combined products produced lower geometric mean anti-Hib-PS antibody levels and a lower percentage of vaccinees exceeded a level of 1.0 μg/mL anti-Hib-PS antibody.[106-108]

The vaccines were reformulated and additional DTaP-Hib-PS conjugate products were studied with attention to chemical interactions and Hib-PS carrier content, and higher anti-Hib-PS carrier content and higher anti-Hib-PS antibody results were observed.[109-112] Relying on induction of memory, the reformulated GlaxoSmithKline combination vaccine later received licensure in Europe and elsewhere, but not in the US. The Wyeth Lederle combination vaccine was studied as a booster,[113] but no additional clinical trials were pursued and their product was not further developed. Aventis Pasteur has since pursued a DTaP five-component vaccine combined with PRP-T,[114] which has been licensed in Canada (Pentacel™).

Authorities in the US differ with authorities in Europe and elsewhere in assessing the significance of lower antibody levels produced by DTaP-Hib-PS conjugate vaccines following primary vaccination. The question under debate related to the pace of activation of memory B and T cells leading to production of antibody and cytokines, respectively, versus the pace of Hib disease pathogenesis from exposure and colonisation to invasion. Although a fair amount of information about immunological memory in mice and rats is available, a paucity of such data in humans are available, especially relating to vaccine responses. Studies with different DTaP-Hib vaccines (GlaxoSmithKline and Aventis Pasteur products) administered at 2, 4 and 6 months of age show priming of the infant immune system to produce anti-Hib-PS memory responses. Even in children with low or undetectable anti-Hib-PS post-primary antibody levels, priming has been demonstrated.[109,112,115,116] The immunological memory response following DTaP-Hib-PS combination vaccination has been carefully analysed.[109,112,115,117,118] It occurs rapidly (4–5 days after Hib-PS or Hib-PS conjugate booster) and is of the IgG class, with antibody of high avidity.[118]

The time required from the moment of initial colonisation of the human nasopharynx with a few Hib bacteria until invasion and bacteraemia follow is unknown. The only information available relates to an infant rat model in which bacteraemia was demonstrated within hours of nasopharyngeal inoculation.[119,120] Unfortunately, the animal model is thought not to be fully applicable to the human situation because the intranasal inoculum used was clearly higher in the animal model than would occur in nature for children. The answers are now coming from countries in Europe, especially the UK, in which the DTaP-Hib-PS conjugate combination vaccine was recently licensed. Hib disease was initially largely eradicated and protection was sustained. However, recent studies reported a rise in Hib disease and a call for boosters.[121] This development is concerning and suggests memory may not be sufficient.

Evaluation of the current expanding immunisation schedule identifies several combination vaccines that could be helpful in reducing the number of immunisations given to infants and young children. In addition to DTaP-Hib, combinations that have been licensed and are under active development include DTaP-HBV, DTaP-inactivated poliovirus vaccine (IPV), DTaP-Hib-IPV, DTaP-IPV-HBV, DTaP-IPV-HBV-Hib and others.[90,122-131]

6. Changing Epidemiology

In the US, Canada, Western Europe and elsewhere, pertussis disease incidence is increasing, despite the introduction and widespread use of DTaP vaccines. Between 1997 and 2000, a total of 29 134 pertussis cases were reported in the US (6564 in

1997, 7405 in 1998, 7298 in 1999 and 7867 in 2000).[132] While the incidence of pertussis rose in all age groups, the greatest increase was found in individuals >5 years of age.[133,134] In the US, the observed increase in reported pertussis cases occurred despite pertussis vaccination coverage levels that are higher than at any other time in the past.[135] Explanations for the increased incidence include: (i) changes in laboratory diagnostic methods; (ii) improved reporting because of greater awareness among physicians about the disease; and/or (iii) a greater number of susceptible adolescents and adults due to waning vaccine-induced immunity.[136,137]

There is now a greater recognition of the fact that clinical manifestations of pertussis in adolescents and adults are atypical and milder than in infants.[138,139] As a consequence, the diagnosis of pertussis is often not made and appropriate antibacterial therapy is not initiated in time to prevent transmission to susceptible infants.[138-142]

Two large surveillance studies tracking pertussis illness in 10- to 49-year-olds showed significant rates and morbidity in this population (table IV).[137,143] In addition to the morbidity, adolescents and adults play a significant role in the transmission of pertussis to infants, who experience a higher incidence of severe complications. A study by Bisgard et al.[144] showed that mothers with pertussis were the most common source of disease for their infants <12 months old. Overall, the most common source of infection for infants was adults >20 years old.

Protection from whole-cell pertussis vaccines wanes progressively after the last dose[145] and during the past decade pertussis has been increasingly recognised in adolescents and adults.[132-137,146] The annual incidence of undiagnosed infections in healthy adolescents is from 6% to 8%[147] and in healthy adults from 29% to 43%.[148] Evaluation of adolescents and adults with cough indicates that *B. pertussis* infection is a common cause. In fact, as many as 20% of adults and adolescents with a cough of 7 days duration have pertussis infection.[149] University students and military personal frequently contract *B. pertussis* infection.[150-153] A large pertussis outbreak in Canada in the year 2000 documented several changes in the illness: (i) a higher incidence among pre-teens and teens than all other age groups; and (ii) a decreasing incidence among infants and preschool children.[154]

Table IV. Morbidity associated with pertussis among adolescents and adults

Symptoms/signs	Minnesota[143]	Massachusetts[137] (%)	
	(%)	adolescents	adults
Paroxysmal cough	100	85	87
Whooping	26	30	35
Post-tussive emesis	56	45	41
Apnoea	–	19	37
Cyanosis	–	6	9
Hospitalisation	0	1.4	3.5

7. Adolescent and Adult Acellular Pertussis Vaccination

The accumulating evidence of the importance of pertussis infection among adolescents and adults, coupled with the low rate of adverse reactions with acellular pertussis vaccines in children, has led to safety, immunogenicity and efficacy trials of acellular pertussis vaccines in adolescents and adults.[76,77,155,156] A US multicentre trial evaluated five acellular pertussis vaccines compared with placebo (figure 2).[156] Three dilutions of the vaccines were administered to adults. In most cases, the highest dose of vaccine was the dose used for primary immunisation of infants. No significant differences in systemic symptoms were noted between the vaccine and placebo groups. Local reactions were common but not severe. Significant increases in antibody levels to vaccine antigens were seen with increasing doses of pertussis antigens for all vaccines. The antibody levels fell 1 year after immunisation but were higher than pre-vaccine levels. In a study from Finland, pertussis-specific antibody and CMI responses were evaluated 8 years after acellular pertussis booster vaccinations. Eight-year postvaccination antibody levels were 3–20 times higher than pre-immunisation levels and CMI responses were significantly higher in vaccinees than controls.[157] A clinical trial comparing an adult DTaP vaccine to DT in Canada showed no signifi-

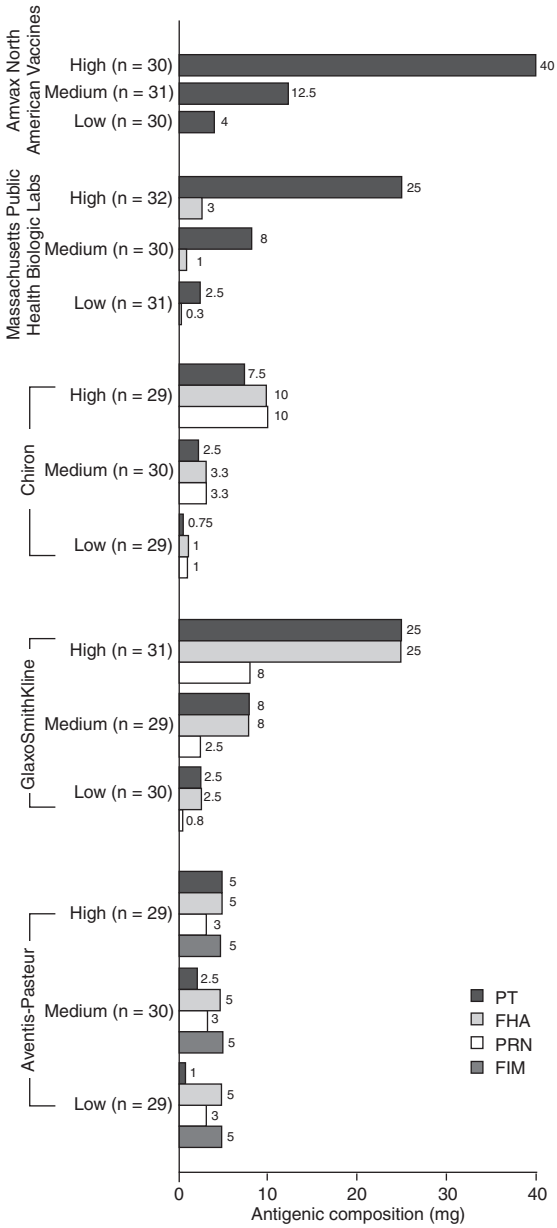

Fig. 2. Adult acellular pertussis vaccine trial: vaccine composition. The aluminium content of each dose of acellular pertussis vaccine was similar. Placebo (n = 31) was isotonic saline containing 0.01% thimersol. **FHA** = filamentous haemagglutinin; **FIM** = fimbrial agglutinogens; **PRN** = pertactin (also known as 69kD); **PT** = pertussis toxoid.

cant differences in local reactions.[158] In 2000, this DTaP vaccine was approved for use in Canada as a booster dose in adolescents and adults 12–54 years of age. Acellular pertussis vaccines are licensed and recommended for booster doses in Germany for 9- to 17-year-olds and in France for 11- to 13-year-olds.[159]

An acellular pertussis vaccine efficacy trial in adolescents and adults using a GlaxoSmithKline three-component (PT, FHA and pertactin) product was completed in the US in 2001. Data from this trial will further help evaluate the efficacy of acellular pertussis vaccines when given as a booster dose.[160] Studies completed thus far have not established whether different vaccine preparations will have differing efficacy.

8. Economic Impact of Pertussis

Pertussis disease morbidity produces a significant cost in children, adolescents, adults, families, hospitals and communities. The economic consequences of pertussis were recently assessed among 107 patients.[161] The average duration of illness before diagnosis was 21 days (range 12–37 days); the average number of physician visits was 3 (range 1–15). Antibacterials were prescribed for 91%; all patients took symptomatic medications. Twenty-eight percent of patients visited a hospital emergency department and 14% were hospitalised. A majority of adults missed work as a result of illness or to care for a sick child. The total direct and indirect cost was estimated to be $US3558 per case for all cases. A re-calculation of the cost per adult case yielded a cost of $US1630 per case (table V; 1992 values).[161]

The cost of pertussis illness in families has been analysed.[162] During an 18-month study, 172 individuals as part of 130 families fulfilled a case definition of pertussis. The average direct medical costs for care of an ill infant, child, adolescent and adult were $US2822, $US308, $US254 and $US181, respectively.[162] Loss of work by adults to care for sick children or from illness themselves, averaged 6 days (range 1–35 days) with an associated additional cost of $US767 per family. The financial effect in total was $US2115 per family (1995 and 1996 values).

Table V. Costs of pertussis illness in a recent US survey[162]

Cost category	Cost/case (1992 US dollars)	
	all cases	adult cases
Physician visits		
direct costs	134	45
indirect costs	122	41
subtotal	256	86
Laboratory tests		
direct costs	24	24
Medications		
antibacterials	110	55
symptomatic	96	48
subtotal	206	103
Emergency department visits		
direct costs	48	43
indirect costs	17	62
subtotal	65	105
Hospitalisation		
direct costs	1651	0
indirect costs	159	0
subtotal	1810	0
Additional childcare	36	0
lost work days	1161	1312
Total	**3558**	**1630**

Decisions regarding recommendations by public health authorities for acellular pertussis booster vaccinations in adolescents and adults are likely to take into consideration cost efficacy. Data from the US Centers for Disease Control and Prevention for 1997–2000 show pertussis-related hospitalisations, complications and death occur in these age groups, albeit infrequently.[163] The major cost of illness in adolescents and especially adults comes from the cost to society of missed work. Two studies found that ill adults missed an average of 8[161] and 6 days' work.[162] More recently, our group studied the work loss and work productivity reduction that occurs when adults contract pertussis.[164] After starting antibacterial treatment it took a median of 9 days (range 2–45 days) before the adults reported symptom improvement and a median of 32 days (range 5–90 days) to report full recovery. Most adults lost at least 1 day of work and the median was 3 lost days (range 0–21 days). Fifty adults completed a survey assessing their productivity while at work: 54% reported that they were <100% productive, with most reporting 50–75% productivity. Reduced productivity persisted for up to 6 weeks for some adults.

Ekwueme et al.[165] examined the economics of DTaP or DTwP vaccination in the US according to the current childhood schedule. Their analysis examined the cost-benefit ratio from both a healthcare system and societal perspective, assuming a 4.1 million patient cohort. Without any pertussis vaccination programme, their model predicted 2.87 million cases and 1131 deaths at a cost of $US4.755 billion to the healthcare system and $US23.56 billion from the societal perspective. From the societal perspective, net savings from the use of acellular pertussis or whole-cell pertussis vaccine was $US4.362 million and $US4.474 million, respectively. The benefit-cost ratios for DTaP from a healthcare system and societal perspective were 9 : 1 and 27 : 1, respectively.

Pertussis is a thoroughly studied, yet at times poorly understood, illness. Despite all that has been learned, much still needs to be discovered.

9. Conclusions

Eight efficacy trials conducted in the early 1990s allow the conclusion that acellular pertussis vaccines are safely used, well tolerated and effective. The relative efficacy of acellular and whole-cell vaccines varies depending upon the case definition of pertussis used. However, three- and five-component acellular vaccines appear to be as or more effective than whole-cell comparators using the WHO definition. Absolute efficacy against mild pertussis appears higher with three- and five-component acellular pertussis vaccines than with one- and two-component vaccines.

The search for a correlate of immunity for pertussis continues. *Post hoc* analyses have suggested that a combination of antibodies to pertactin and fimbriae (key agglutinogens of the organism) may be the best correlates; however, since *B. pertussis* is a mucosal pathogen (and mucosal immunity was not assessed in the efficacy trials), a clear serological correlate may not emerge. When booster immunisations have been administered in children, they have been associated with a 1–2% occurrence of large

local reactions. The data suggest that a reduction in antigen content may obviate this minor but measurable safety concern.

In the follow-up that has occurred from the efficacy trials, it does appear that pertussis immunity is sustained for several years following acellular pertussis vaccination in infancy. Paradoxically, the persistence of efficacy appears to occur in the absence of sustained antibody levels, which suggests that serum antibody levels may not be of primary importance. The importance of T-cell immunity remains controversial.

Combination vaccines with acellular pertussis products would be desirable to simplify immunisation schedules, and DTaP combination products have been licensed in many countries. Safety and immunogenicity have generally been similar to that achieved with the individual vaccines. However, an exception appears to occur with the combined administration of currently available DTaP/Hib vaccines, in that lower levels of immunity may have led to an increase in Hib disease in the UK where this product received widespread application.

The incidence of pertussis is increasing despite the introduction and widespread use of DTaP vaccines. While the incidence has been rising in all age groups, the greatest increase has occurred in individuals over the age of 5 years. The main proposed explanation for the increasing occurrence of pertussis in the older age groups includes improved diagnostic methods, greater awareness among physicians and waning vaccine-induced immunity. As a consequence, adolescent and adult acellular pertussis vaccine formulations have been developed and shown to be safely used, immunogenic and efficacious in adolescent and adult populations. Licensure has occurred in some countries and is anticipated in other countries in the near future. We recommend that adolescent/adult DTaP vaccines should be used but decisions regarding recommendations by public health authorities for acellular pertussis booster vaccinations in adolescents and adults are likely to take into consideration cost efficacy.

Future research is likely to involve the evaluation of other candidate immunogens for inclusion in acellular pertussis vaccines. Further study of mechanisms of immune protection is needed and should focus on T-cell and mucosal immunity. A clearer understanding of the cause of large local reactions on boosting with DTaP vaccines should allow a solution to resolve this safety concern. A DTaP-Hib combination vaccine that does not suppress Hib conjugate vaccine immune responses needs to be found. A cost-effective strategy for introduction and widespread use of DTaP vaccines in adolescents and adults should prove beneficial to the vaccinees and vulnerable infants.

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