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Developing Better Paediatric Vaccines

The Case of Pertussis Vaccine

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Abstract

After 2 decades of development, acellular pertussis vaccines are becoming more widely available for use. Products that contain from 1 to 5 purified antigens of *Bordetella pertussis* have been assessed in safety, immunogenicity and efficacy studies and are licensed in an increasing number of countries. All acellular pertussis vaccines are associated with fewer local and systemic adverse reactions than the whole-cell pertussis vaccines that have been used for the last 50 years. The acellular pertussis vaccines elicit an antibody response that is generally equivalent to that seen with the whole-cell pertussis vaccines. The acellular pertussis vaccines are effective; using a case-definition of paroxysmal cough of 21 or more days and laboratory confirmation of pertussis, protective efficacy was variable but in excess of 70% for most products. Relative efficacy of the acellular pertussis vaccines and the whole-cell pertussis vaccines was also variable, depending on the products involved and the study design. The choice of antigen content for acellular pertussis vaccines is controversial. Although there are pro-

ponents of a monocomponent pertussis toxoid vaccine, the weight of evidence suggests that multicomponent vaccines containing pertussis toxoid and filamentous haemagglutinin and pertactin are more effective than 1- or 2-component vaccines, and that the addition of fimbriae may provide additional protection against less severe disease.

Acellular pertussis vaccines are all available in combination with diphtheria and tetanus toxoids; some products also contain inactivated poliovirus vaccine and *Haemophilus influenzae* b–conjugate vaccine or hepatitis B vaccine. Not all acellular pertussis vaccines are available in these larger combinations because of difficulties with decreased antibody response to one or more antigens in the combined product.

Future directions for research into acellular pertussis vaccines include optimisation of antigen content and administration schedule, and further development of multicomponent vaccines.

Diphtheria, tetanus and pertussis vaccines (DTP) have been available for over half a century and form the backbone of childhood immunisation programmes worldwide. In this review, the history and current status of the use of DTP will be briefly summarised, and recent advances in their formulation will be discussed. Although the resurgence of diphtheria in Eastern Europe in countries of the former Soviet Union underscores that this disease has not been conquered, there have not been major modifications of the highly effective diphtheria and tetanus toxoids. Therefore, this review will focus on the pertussis component of the vaccine which has undergone major modifications and improvements over the last decade. Particular emphasis will be given to the acellular pertussis vaccines which are now available in many countries.

1. History

Active immunisation against diphtheria became widely used in some countries in the early part of this century, first with a toxin-antitoxin mixture and later with diphtheria toxoid. By the 1920s it was known that increased immunogenicity could be achieved by absorption of the toxoid onto aluminium salts. Tetanus antitoxin became available in the 1930s and was widely used by the military during the Second World War. Pertussis vaccines were also developed in the first half of the century from preparations of inactivated whole bacterial cells. The efficacy of these vaccines was demonstrated in studies sponsored by the British Medical Research Council[1] and efficacy was correlated with pertussis agglutinative titres.[2]

By the mid 1940s combination vaccines that included diphtheria and tetanus toxoids and whole-cell pertussis vaccines became available and were soon recommended for universal use in many industrialised countries. Over 50 years later, essentially the same vaccines are in current use.

The decade of the 1970s witnessed 2 divergent events. In industrialised countries which had seen dramatic decreases in the incidence of pertussis (and the virtual disappearance of diphtheria and tetanus), concerns about pertussis vaccine–associated adverse events led to decreased use of DTP and a resulting resurgence in the incidence of pertussis.[3,4] In contrast, as a result of the Expanded Program on Immunisation initiated by the World Health Organization (WHO) in the 1970s, global coverage with DTP rose from only 5% of eligible children at the inception of the programme to the current status approaching 80%.

Driven by the concern of serious adverse events and an increase in the understanding of the pathogenesis of pertussis and immunity to *Bordetella pertussis*, acellular pertussis vaccines made from purified virulence factors were developed in Japan. These vaccines were licensed in Japan in 1981 and replaced the whole-cell pertussis vaccines. The efficacy of acellular pertussis vaccines was examined in a large clinical trial in Sweden in the 1980s and

in a series of studies completed in the last several years.

2. Acellular Pertussis Vaccine Development

After their initial development and introduction in Japan, acellular pertussis vaccines are now produced by many manufacturers and are available in many countries. This review is not meant to be an exhaustive catalogue of all products currently in use throughout the world but rather a review of those products for which data are available in the scientific literature. Indeed, this criterion may not correlate well with vaccine availability in the marketplace.

2.1 Early Development

The major impetus for the development of new acellular pertussis vaccines was a concern about severe whole-cell pertussis vaccine–associated adverse events which may have been unrelated to the vaccine. In Japan, mandatory pertussis immunisation had been in place since 1947 with a resultant decrease in the incidence of pertussis.[5] As in other developed countries during the 1970s, the decreased incidence of the disease coupled with the concern about vaccine adverse effects led to discussions on whether pertussis immunisation should be continued. In 1974, 2 infants died in Japan within 48 hours of receiving pertussis vaccine; pertussis immunisation was suspended while the cases were being investigated. Although immunisation was reinstituted (albeit at an older age) several months later, rates of immunisation never recovered and cases of pertussis began to increase. By 1979, over 13 000 cases and 41 deaths from pertussis were reported.[3]

Concurrent with the suspension of pertussis immunisation, a concerted laboratory effort to identify protective antigens of *B. pertussis* and to develop safer pertussis vaccines was begun which culminated in clinical trials in Japan between 1978 and 1981.[6] Although 6 manufacturers in Japan were involved in the production of these vaccines, 2 types of vaccines were produced using similar technology; these are named after the major manufacturer.

The Biken-type vaccine contains nearly equal quantities of pertussis toxoid (PT) and filamentous haemagglutinin (FHA). The Takeda-type vaccine contains primarily FHA with some PT and agglutinogens. These vaccines were introduced for mass immunisation in Japan in 1981. Although safety and immunogenicity were demonstrated in clinical trials in Japan prior to approval for use,[6] licensure in Japan was based on meeting minimum requirements for purity and potency[5] rather than on clinical efficacy studies. After the introduction of the acellular pertussis vaccines in Japan, studies assessing their safety and immunogenicity were performed[7,8] and several household contact and epidemiological studies evaluated the efficacy of the vaccines, although the specific vaccine used was often not mentioned.[9-14] The vaccines were clearly efficacious compared with no immunisation and the incidence of pertussis again declined in Japan.

2.2 Current Product Review (Safety, Immunogenicity, Efficacy)

With the success of the acellular pertussis vaccines in Japan, other countries attempted to learn from this experience and determine what data would be required for licensure and implementation.[3] It became clear that in North America and Europe, potency as measured by the mouse intracerebral test would generally not be sufficient for licensure. Instead, well controlled safety, immunogenicity and efficacy studies were required prior to a vaccine's approval for routine use. The results of such studies for different vaccine products are presented in this section. Most studies used the WHO case definition (21 days of paroxysmal cough with laboratory confirmation or variation of this definition[15]) as the primary efficacy indicator. Table I summarises the antigen content for these vaccines.

2.2.1 Biken

The Biken vaccine (Pasteur-Mérieux-Connaught-Biken in the US) contains equal amounts (23.4μg) of PT and FHA and does not contain

Table I. Composition of acellular pertussis vaccines

Vaccine manufacturer	Vaccine composition (μg antigen)				Available commercially
	pertussis toxoid	filamentous haemagglutinin	pertactin	fimbriae 2 and/or 3	
Amvax	40	-	-	-	Yes
Swiss Serum and Vaccine Institute	50	-	-	-	No
Massachusetts Biologic Laboratories	25	-	-	-	No
Pasteur-Mérieux-Connaught-Biken (US)	23.4	23.4	-	-	Yes
Pasteur-Mérieux-Connaught (France)	25	25	-	-	Yes
Michigan Department of Health	25	25	-	-	No
SmithKline Beecham	25	25	-	-	No
SmithKline Beecham	25	25	8	-	Yes
Chiron	5	2.5	2.5	-	Yes
Porton Products	10	10	-	10	No
Wyeth-Lederle-Takeda	3.5	35	2	0.8	Yes
Pasteur-Mérieux-Connaught (Canada)	10[a]	5[a]	3	5	Yes

a In the second Swedish efficacy study[16] and in the currently marketed product, the formulation contains 20μg each of pertussis toxoid and filamentous haemagglutinin.

agglutinogens.[17] After its introduction in Japan, further studies of its safety and immunogenicity were undertaken in Sweden, where immunisation with whole-cell pertussis vaccine had been discontinued in 1979 with a resultant resurgence in disease.[4]

Evaluation of the Biken vaccine in infants[18] demonstrated that it produced fewer local or systemic adverse reactions compared with a primary series with the whole-cell vaccine. Local adverse reactions, however, were more common in children primed and boosted with the acellular pertussis vaccine compared to those primed with whole-cell vaccine and boosted with the acellular vaccine.[19] The acellular vaccine was immunogenic and although antibody levels diminished with time, antibody was still present in over 90% of participants 16 months after a primary series.[20]

These safety and immunogenicity studies were followed in Sweden by the first prospective clinical trial of the efficacy of an acellular pertussis vaccine. Two acellular pertussis vaccines were studied: the PT/FHA vaccine containing 7.5μg protein nitrogen/ml of each antigen in use in Japan, produced by Biken, and a monocomponent PT vaccine also produced by Biken (containing 50% more PT) which had demonstrated a similar safety profile to that of the PT/FHA vaccine in a preliminary phase II study.[21] Follow up of children in the latter study revealed low rates of pertussis after household or daycare exposure.[22]

In the prospective, randomised, placebo-controlled phase III efficacy study,[23] 5- to 11-month-old children received the first of 2 doses of placebo (n = 954), the PT vaccine (n = 1428) or the PT/FHA vaccine (n = 1419). After 15 months of follow up for a cough illness of any duration confirmed by culture, vaccine efficacy was estimated to be 54% [95% confidence interval (CI) 26 to 72%] for the PT vaccine and 69% (95% CI 47 to 82%) for the PT/FHA vaccine. Both vaccines were more efficacious against more severe disease (79 and 80% against culture-confirmed pertussis of over 30 days' duration) and provided moderate protection against household exposures to pertussis.[24] Secondary analyses using serological definitions of pertussis further supported the superiority of the PT/FHA vaccine, particularly against milder disease.[25] Long term protection was demonstrated during 3 years of unblinded passive surveillance, although the differences in protection afforded by the 2 vaccines became more pronounced, with a relative risk of culture-confirmed pertussis of 1.5

(95% CI 1.0 to 2.4) for the PT vaccine group compared with the PT/FHA group.[26]

Concurrent with the Swedish studies, clinical trials were performed to examine the safety and immunogenicity of the Biken vaccine schedule commonly used in North America (3-dose infant primary series, reinforcing dose in the second year, booster dose pre-school). The Biken vaccine used in Japan and that used in the US produced similar antibody responses and adverse reactions.[27] The acellular vaccine consistently caused less erythema, swelling, tenderness, irritability and fever than whole-cell pertussis vaccine when given as a primary infant series[28] or a reinforcing or booster dose to children previously primed with 3[29,30] or 4[31] doses of whole-cell pertussis vaccine. In contrast to the findings in Sweden, no differences in local or systemic adverse events were found between children primed with whole-cell or acellular pertussis vaccine given a reinforcing dose of acellular pertussis vaccine.[32]

The efficacy of 3 doses of the Pasteur-Mérieux-Connaught-Biken PT/FHA vaccine combined with diphtheria and tetanus toxoids was recently assessed in an unblinded case-control study in Germany.[33] Over 16 000 infants received, according to parental choice, either the acellular DTP vaccine (DTaP) containing the Biken PT/FHA pertussis component, licensed whole-cell German DTP, diphtheria and tetanus toxoids (DT) or no vaccine. Prospective surveillance was carried out over 15 months for all coughs lasting 7 days or longer. Vaccine efficacy was 82% (95% CI 68 to 90%) for the acellular vaccine and 96% (95% CI 78 to 99%) for the whole-cell vaccine. Protection against typical disease (21 days or more or paroxysmal cough) was 96% and 97% respectively.

2.2.2 Takeda

The Takeda-type vaccine produced by Takeda Chemical Industries in Osaka, Japan (Wyeth-Lederle-Takeda outside of Japan) contains 35μg FHA, 3.5μg PT, 0.8μg fimbria 2, and 2μg pertactin (PRN).[34] As previously discussed, its efficacy was inferred by the reduction in pertussis after introduction of acellular pertussis vaccine in Japan.[9-14] In a household contact study in Japan, vaccine efficacy was estimated to be 98% against classical pertussis and 81% against 'probable' pertussis.[35]

Safety, immunogenicity and efficacy studies in young infants were subsequently undertaken in North America and Europe using 3-, 4-, and 5-dose series in use in these regions. Both the Japanese and the American formulations of the Takeda acellular vaccine had similar safety profiles and produced similar antibody responses.[36] As with all of the acellular pertussis vaccines tested to date, the Takeda vaccine combined with DT was associated with fewer local and systemic adverse events and produced equal or better antibody response than whole-cell pertussis vaccines in infants undergoing their primary series[37,38] and in pre-school[39-41] and 18-month-old[38,39,41-45] children previously primed with 3 or 4 doses of a whole-cell pertussis vaccine. Adverse events were few and the antibody response was vigorous when the acellular vaccine was given as a fourth dose in children previously primed with the same vaccine.[38] The Takeda vaccine was also well tolerated and immunogenic as a monovalent vaccine (not combined with DT) used as a 'catch up' vaccine in children 15 months to 6 years of age who had not previously received a pertussis vaccine.[46]

The efficacy of the Takeda acellular pertussis vaccine combined with diphtheria and tetanus toxoids was assessed in a longitudinal cohort study in which infants were randomised to receive either 4 doses of a whole-cell DTP or the acellular DTaP or were enrolled in an open 3-dose DT arm based on parental preference.[47] Over 10 000 children were immunised (4273 in the DTaP group, 4259 in the whole-cell DTP group and 1739 in the DT group). Efficacy against typical pertussis (21 days or more of cough with either paroxysms, whoop or post-tussive vomiting) was 93% (95% CI 89 to 96%) in the whole-cell DTP group and 83% (95% CI 76 to 88%) in the DTaP group. Efficacy was lower against milder disease (7 or more days of cough) for both the whole-cell pertussis DTP (83%; 95% CI 76 to 88%) and the DTaP (72%;

95% CI 62 to 79%). The efficacy of the acellular pertussis vaccine was substantially lower after 3 doses (62% for cough of 7 days or longer).

The efficacy of the Wyeth-Lederle-Takeda acellular pertussis vaccine was further evaluated in a household contact substudy of the prospective cohort study.[48] In this study, the efficacy of the whole-cell pertussis vaccine against cough of 7 or more days' duration was 84% (95% CI 65 to 93%) and 58% (95% CI 30 to 75%) for the acellular pertussis vaccine. Similar to the main study, the efficacy against more severe infection was higher in both groups (94%, 95% CI 77 to 99%; and 86%, 95% CI 62 to 95%, respectively).

2.2.3 Amvax

The acellular pertussis vaccine manufactured by Amvax is the only pertussis vaccine currently available which contains only PT. Pertussis toxin inactivated by hydrogen peroxide was found to have low reactogenicity in initial trials in healthy adults.[49] The vaccine was well tolerated and immunogenic when given as a 2- or 3-dose regimen to 18- to 23-month-old children who had not previously received a pertussis immunisation[50] and in 18-month-old infants previously given 3 doses of whole-cell pertussis vaccine.[51] Safety and immunogenicity of the PT vaccine were further assessed using 3-, 5-, 7-month and 3-, 5-, 12-month schedules.[52] Local adverse reactions to PT were similar to reactions with a diphtheria-tetanus toxoid vaccine given in the opposite limb. Higher antibody levels were elicited by the 3-, 5-, 12-month schedule although these differences had mostly disappeared by 3 years of age. Efficacy of the vaccine was estimated using parental recall of pertussis-like symptoms in vaccine recipients and age-matched controls; none of the vaccinated children had clinically defined pertussis compared to 20% of the controls.

A placebo-controlled clinical trial to measure the efficacy of the Amvax cellular pertussis vaccine was undertaken in Sweden.[53] Over 3400 infants were randomly allocated to receive the acellular DTaP or DT alone using a 3-, 5- and 12-month immunisation schedule. After a median of 17.5 months, the efficacy of the acellular pertussis vaccine was 71% (95% CI 63 to 78%) against laboratory-confirmed pertussis with paroxysmal cough of 21 days or more and 54% (95% CI 42 to 63%) for laboratory-confirmed pertussis with paroxysmal cough of 7 days or more. A household contact substudy[54] performed as part of the larger clinical trial revealed an efficacy of 75% (95% CI 64 to 84%). Vaccine efficacy was lower in children who had only received the first 2 primary doses (66%; 95 CI 15 to 90%). An additional 6-month open follow-up of both studies indicated that the vaccine continued to be protective in both the community (efficacy 77%, 95% CI 66 to 85%) and household (efficacy 76%, 95% CI 51 to 91%) settings.[55]

2.2.4 Pasteur-Mérieux-Connaught (France)

Pasteur-Mérieux-Connaught (Lyon, France) produces a 2-component PT/FHA vaccine which was demonstrated to be well tolerated and immunogenic when given to 2-month-old infants receiving their 3-dose primary series,[56,57] 18-month-old infants[56] and pre-school children[56] previously primed with 3 or 4 doses of whole-cell pertussis vaccine, and in 19-month-old infants previously primed with either whole-cell or acellular pertussis vaccine.[58] Using a formulation containing 25µg PT and 25µg FHA, vaccine efficacy was compared with a whole-cell pertussis vaccine in a randomised, double blind study in Senegal.[59] The relative risk of pertussis in the acellular pertussis vaccine compared with the whole-cell pertussis vaccine group was 1.54 (95% CI 1.23 to 1.93). The acellular pertussis vaccine performed less well with time; the relative risk was 1.16 (95% CI 0.77 to 1.73) in children younger than 18 months and 1.76 (95% CI 1.33 to 2.33) in children older than 18 months. Absolute efficacy, estimated in a nested case-contact study, was 85% (95% CI 66 to 93%) for the acellular pertussis vaccine and 96% for the whole cell vaccine using the case definition of laboratory confirmed pertussis with paroxysmal cough of 21 or more days.

2.2.5 SmithKline Beecham

The acellular pertussis vaccine manufactured by SmithKline Beecham (Rixensart, Belgium) is a 3-

component product consisting of PT (25μg), FHA (25μg) and PRN (8μg), although early formulations included only PT and FHA[60] or contained a lower (8μg) PT content.[61] The vaccine was associated with fewer adverse reactions and elicited higher antibody levels than whole-cell vaccines in infants undergoing the primary immunisation series at 2, 4 and 6 months in the US.[60,62]

In a large safety and immunogenicity study in Germany, over 22 000 infants were vaccinated with the acellular pertussis vaccine at 3, 4 and 5 months. The vaccine was well tolerated and induced an antibody response against all pertussis antigens.[63] Lower rates of adverse events and higher antibody responses were observed in 15- to 20-month-old infants previously immunised with whole-cell pertussis vaccine who received a booster of the acellular pertussis vaccine than in infants who received whole-cell vaccine for initial and booster immunisations.[64,65] Similar results were found in pre-school children receiving their fifth dose of vaccine.[64,66] Adverse events increased in frequency with a fourth dose of the acellular pertussis vaccine, with a small proportion of recipients (1.1%) reporting a nonpainful, nonerythematous swelling of the entire thigh.[67]

The efficacy of the SmithKline Beecham acellular pertussis vaccine was demonstrated in several clinical trials. In a household contact study of over 22 000 German infants immunised at 3, 4 and 5 months of age, 360 evaluable cases of pertussis occurred in study households. Efficacy of the 3-component pertussis vaccine in children who had been in contact with infected individuals was calculated at 88.7% (95% CI 76.6 to 94.4%) during the period prior to the recommended booster dose using a case definition of 21 days of paroxysmal cough with laboratory confirmation.[68]

In a randomised, placebo controlled clinical trial in Italy, the efficacy of the 3-component vaccine given to 4481 infants was 84% (95% CI 76 to 89%), using a case definition of 21 days of paroxysmal cough with laboratory confirmation.[69] In the same study, an American whole-cell vaccine had an efficacy of only 36% (95% CI 14 to 52%).

The importance of PRN in the protective efficacy of the SmithKline Beecham vaccine was suggested in a similarly designed clinical trial in Sweden in which the 2-component SmithKline Beecham (PT/FHA) vaccine was studied, along with the same whole-cell pertussis vaccine control. In this study,[70] the 2-component acellular pertussis vaccine given to 2538 infants had a protective efficacy of 58.9% (95% CI 50.9 to 65.9%); the efficacy of the whole-cell vaccine was 48.3% (95% CI 37.0 to 57.6%). Similar differences were observed in the second phase of the Swedish efficacy study[16,71] where the relative risk of pertussis after a PRN-containing 3 component vaccine manufactured by Chiron was about half that with the 2-component SmithKline Beecham vaccine (RR 0.4, 95% CI 0.24 to 0.66).

2.2.6 Chiron

The vaccine produced by Chiron (Siena, Italy) is the only acellular pertussis vaccine currently in production that uses recombinant technology. In this vaccine the pertussis toxin is genetically detoxified by amino acid substitutions at positions 9 and 129.[72] The detoxified PT was found to be both well tolerated and immunogenic in adults[73] and infants and toddlers.[74] A 3-component formulation (FHA, PRN and genetically inactivated PT) was also found to be well tolerated and immunogenic in adults[75] and in infants and toddlers.[76] A formulation containing smaller amounts of pertussis antigens (PT, 5μg; FHA 2.5μg; PRN, 2.5μg) was also associated with fewer adverse events and higher antibody levels than a whole-cell pertussis vaccine in 2-month-old infants immunised at 2, 4 and 6 months of age.[77] This vaccine was also well tolerated and immunogenic in these same infants given a booster dose of the acellular vaccine at 15 to 21 months of age.[78] In another study, the Chiron vaccine was associated with fewer adverse events and was more immunogenic than a whole-cell vaccine in infants undergoing their first 3-dose series; at the time of the booster, the Chiron acellular vaccine had similar rates of adverse events and antibody response as the Wyeth-Lederle-Takeda control acellular pertussis vaccine.[79]

The efficacy of the Chiron vaccine was evaluated in 2 randomised controlled trials. The first was the same Italian efficacy study that evaluated the 3-component SmithKline Beecham vaccine.[69] In this study, the Chiron 3-component recombinant PT vaccine (PT, 5μg; FHA 2.5μg; PRN, 2.5μg) given to 4452 infants had an identical protective efficacy (84%, 95% CI 76 to 90%) to that of the 3-component SmithKline Beecham vaccine. The Chiron vaccine was also included in the second phase of the Swedish efficacy study, in which it had similar efficacy to a control whole-cell vaccine for culture-confirmed pertussis with paroxysmal cough of 21 days or more (RR 1.38, 95% CI 0.71 to 2.69)[71] and was more protective than a 2-component (PT/FHA) acellular pertussis vaccine (SmithKline Beecham; RR 0.4, 95% CI 0.24 to 0.66).

2.2.7 Pasteur-Mérieux-Connaught (Canada)

The Pasteur-Mérieux-Connaught (Canada) acellular pertussis vaccine is a 5-component vaccine containing PT, FHA, PRN and fimbriae 2 and 3. The vaccine formulated with and without PRN was found to be well tolerated and immunogenic in toddlers and pre-school children with no incremental reactogenicity with the addition of PRN[80] and in toddlers with varying quantities of the constituent antigens.[81] Infants immunised with 4 doses of the acellular pertussis vaccine containing 10μg PT, 5μg FHA, 3μg PRN and 5μg of fimbriae 2 and 3 had fewer adverse events and higher antibody levels than those immunised with the whole-cell pertussis vaccine.[82] A vaccine formulation with twice the PT content (20μg) and 4 times the FHA content (20μg) was not associated with any increase in adverse reactions.[83]

The efficacy of the 5-component pertussis vaccine was demonstrated in both phases of the Swedish efficacy study. In the first phase, the vaccine formulation with lower antigen content had an efficacy of 85.2% (95% CI 80.6 to 88.8%) when given to 2551 infants, significantly higher than both the American whole-cell pertussis vaccine control and the SmithKline Beecham 2-component acellular pertussis vaccine.[70] In the second phase, using the higher antigen content formulation given to over 20 000 infants, the protective efficacy of the 5-component vaccine against culture-proven pertussis with paroxysmal cough of 21 days or more was equivalent to that of the Chiron 3-component vaccine and the whole-cell control vaccine and superior to that of the SmithKline Beecham 2-component vaccine.[16] However, the 5-component vaccine was more protective than the 3-component vaccine against milder disease (culture-proven with any duration of cough); together with data from the earlier Swedish and Italian efficacy studies (in which the 5-component vaccine was more protective than the 3-component vaccine against pertussis with a case definition of 7 or more days of cough[69,70]), this suggests an important role for fimbriae in protection against milder disease.

2.2.8 Other Acellular Pertussis Vaccines

The safety and immunogenicity of several other acellular pertussis vaccines have been studied. A PT and a PT/FHA acellular pertussis vaccine manufactured by the Michigan Department of Public Health were compared with a whole-cell vaccine and found to be associated with fewer adverse events; the anti-PT antibody response to the 2-component vaccine was diminished compared with the monovalent PT vaccine.[84] A 4-component acellular pertussis vaccine consisting of PT, FHA, and fimbriae 2 and 3 manufactured by the Centre for Applied Microbiology and Research (later Porton Products) in the UK was associated with fewer systemic adverse reactions and higher antibody levels than the whole-cell pertussis vaccine.[85] A PT monocomponent vaccine prepared by the Massachusetts Public Health Laboratories was included in a study of multiple acellular pertussis vaccines in comparison to 3 American whole-cell vaccines for the booster dose in the second year of life and pre-school.[86] Another PT vaccine made by the Swiss Serum and Vaccine Institute was studied in a multicentre study of 13 acellular pertussis vaccines compared with 2 American whole-cell pertussis vaccines.[34,87,88] The efficacy of acellular pertussis vaccines from

these 4 manufacturers has not been assessed and they are not licensed for use in any country.

2.3 Overview of Safety, Immunogenicity and Efficacy

All of the pertussis vaccines currently in use are associated with fewer adverse events than whole-cell pertussis vaccines. Differences in vaccine-associated adverse events amongst the acellular pertussis vaccines are minimal and unlikely to be of clinical significance. Comparison of products studied in different trials is difficult; however, several multicentre studies of the safety and immunogenicity of multiple acellular pertussis vaccines were sponsored by the United States National Institute of Allergy and Infectious Disease and these trials allow some comparisons to be made. In the first study, 9 acellular pertussis vaccines and 3 whole-cell pertussis vaccines were compared as a booster dose in the second year of life or pre-school after 3 or 4 previous doses of whole-cell pertussis vaccine. All of the acellular pertussis vaccines were associated with fewer adverse events and were as immunogenic as or more immunogenic than the whole-cell vaccines.[86]

In a second study, in 2-, 4- and 6-month-old infants, adverse reactions after 13 acellular pertussis vaccines were again significantly less frequent than after the whole-cell pertussis vaccine; differences between the vaccines were detected but were not judged to be of sufficient importance to favour one product over another.[88] Table II summarises data from this study for selected adverse reactions and vaccines. The antibody response to all antigens contained in the vaccines was similar to the responses to whole-cell pertussis vaccines. Differences amongst the acellular pertussis vaccines were not directly correlated with the antigen content of the vaccine.[34] Table III summarises the immunological data from this study for selected vaccines reviewed. In a follow-up study of members of this cohort who received a fourth dose as either acellular or whole-cell pertussis vaccine,[87] acellular pertussis vaccines were again associated with fewer adverse events and similar antibody levels to whole-cell vaccines. Again, there was no direct correlation between antibody content and antibody level elicited. No acellular pertussis vaccine was consistently associated with fewer adverse events or higher antibody levels.

The relative efficacy of the acellular pertussis vaccines is even more difficult to assess because of differences in design of the pivotal efficacy studies (e.g. case definitions, control vaccines) together with differences in geography and epidemiology (table IV). However, some 'soft' conclusions are suggested from studies in which more than one acellular pertussis vaccine was included and from studies that were similarly designed to allow bridging of the study results. All acellular vaccines currently available contain PT; most also contain FHA. In the initial Swedish efficacy studies in the 1980s, the data indicated that a PT/FHA vaccine was superior to a PT monocomponent vaccine.[23]

Table II. Adverse reactions reported after immunisation with selected[a] acellular pertussis vaccines during a multicentred multivaccine study[88]

Vaccine (composition)[a]	Adverse events reported (%) in the 3 days after any of the 3 primary doses						
	redness >20mm	swelling >20mm	pain ≥moderate	fussiness ≥moderate	fever >101°F (38.5°C)	drowsiness	anorexia
Pasteur-Mérieux-Connaught-Biken (US)	5.2	3.7	9.6	19.3	5.2	41.5	22.2
Pasteur-Mérieux-Connaught (France)	4.5	5.3	8.3	12.0	4.6	42.1	20.3
SmithKline Beecham (2-component)	2.1	4.2	6.2	17.2	3.1	37.0	17.7
SmithKline Beecham (3-component)	4.2	5.8	10.8	15.0	3.3	46.7	19.2
Chiron	1.6	2.4	1.6	11.9	1.6	41.3	19.0
Wyeth-Lederle-Takeda	2.8	3.2	3.7	14.3	3.2	40.6	24.9
Pasteur-Mérieux-Connaught (Canada)	3.6	4.4	5.1	18.2	3.6	42.3	19.0
Whole-cell vaccine (Lederle)	16.4	22.4	40.2	41.5	15.9	62.0	35.0

a Content of vaccines is presented in Table I; selected vaccines are those included in the study for which efficacy data are now available.

Table III. Geometric mean antibody levels after immunisation with selected[a] acellular pertussis vaccines during a multicentre multivaccine study[34]

Vaccine (composition)[a]	Geometric mean antibody levels (95% confidence intervals) post-immunisation (dose 3)				
	pertussis toxoid	filamentous haemagglutinin	pertactin	fimbriae	agglutinins
Pasteur-Mérieux-Connaught-Biken (US)	127 (111-144)	85 (73-95)	3.5 (3.2-3.9)	2.0 (1.7-2.3)	9 (8-11)
Pasteur-Mérieux-Connaught (France)	68 (60-76)	143 (126-161)	3.3 (3.1-3.6)	1.9 (1.6-2.1)	8 (7-10)
SmithKline Beecham (2-component)	104 (94-116)	110 (99-122)	3.3 (3.1-3.5)	1.9 (1.7-2.1)	9 (8-10)
SmithKline Beecham (3-component)	54 (46-64)	103 (88-120)	185 (148-231)	1.9 (1.7-2.2)	16 (14-19)
Chiron	99 (87-113)	21 (18-25)	65 (53-79)	1.9 (1.7-2.1)	8 (7-9)
Wyeth-Lederle-Takeda	14 (12-17)	144 (127-163)	54 (47-62)	51 (41-63)	48 (41-56)
Pasteur-Mérieux-Connaught (Canada)	36 (32-41)	37 (32-42)	114 (93-139)	240 (204-282)	73 (60-89)
Whole-cell vaccine (Lederle)	67 (54-83)	3.0 (2.7-3.4)	63 (54-74)	191 (161-227)	83 (72-96)

a Content of vaccines is presented in Table I; selected vaccines are those included in the study for which efficacy data are now available.

In a more recent study of the hydrogen peroxide–inactivated PT vaccine, the point efficacy estimate was the lowest of any of the recent randomised controlled trials.[53] Higher point estimates of efficacy were demonstrated in some studies using case contact design with the French Pasteur-Mérieux-Connaught vaccine[59] and unblinded case-control design with the American Pasteur-Mérieux-Connaught-Biken vaccine.[33] However, in randomised controlled trials where 2- or multicomponent vaccines were used in similarly designed studies[69,70] or in the same study,[71] a 3-component vaccine (PT, FHA, PRN) or a 5-component vaccine (PT, FHA, PRN, fimbriae 2 and 3) was more protective than a 2-component (PT, FHA) vaccine. Finally, the addition of fimbriae to PT, FHA and PRN in the multicomponent vaccines appears to improve the protection against milder disease.[70,71]

2.4 Combinations with Other Antigens

A high priority has been placed on developing products that combine other antigens routinely given to infants with the acellular DTaP 'backbone'. These additional antigens include inactivated poliovirus vaccine, *Haemophilus influenzae* b conjugate vaccine (Hib), and hepatitis B vaccine. To date, progress toward this objective has been slow and inconsistent.

2.4.1 DTaP and Hepatitis B Vaccine

A vaccine that combines the DTaP with hepatitis B vaccine would be useful in the many countries worldwide that have implemented universal infant hepatitis B immunisation programmes. The feasibility of the combination was demonstrated with the SmithKline Beecham 3-component vaccine and the recombinant hepatitis B vaccine from this manufacturer.[89,90] A larger study compared the combined DTaP–hepatitis B vaccine given at 2, 4 and 6 months and given at 3, 5 and 11 months and found both schedules to be well tolerated and immunogenic, although a separate injection control group was not included.[91]

2.4.2 DTaP and Inactivated Poliovirus Vaccine

In countries where inactivated poliovirus vaccine (IPV) is routinely used, a combination vaccine with DTaP would decrease the number of injections required at each immunisation visit. IPV was successfully combined with the 5-component DTaP produced by Pasteur-Mérieux-Connaught (Canada)[92] and the 3-component vaccine produced by SmithKline Beecham.[93] A combination of the French Pasteur-Mérieux-Connaught 2-component acellular pertussis vaccine and IPV resulted in decreased antibody levels against the pertussis antigens, diphtheria and tetanus compared with the DTaP without IPV.[94]

2.4.3 DTaP and Haemophilus Influenzae b Conjugate Vaccine

Combining acellular pertussis vaccine with Hib vaccine has been more problematic for vaccine manufacturers because of decreased antibody response to Hib with the combination. In several studies, the Hib-tetanus toxoid conjugate vaccine induced lower Hib antibody levels after reconstitution with the SmithKline Beecham 3-component DTaP vaccine than when the 2 vaccines were given separately.[95,96] Similar diminution in Hib antibody response was demonstrated when the Hib-tetanus toxoid vaccine was reconstituted with the Pasteur-Mérieux-Connaught-Biken 2-component pertussis vaccine[97] and with a combined Wyeth-Lederle-Takeda acellular pertussis vaccine/Hib diphtheria toxoid (HbOC) conjugate vaccine.[98] The clinical relevance of these findings has not been established. In some studies, such as that using the 5-component Canadian Pasteur-Mérieux-Connaught DTaP vaccine to reconstitute the Hib-tetanus toxoid conjugate vaccine for the 18 month booster dose, there were differences in response between single and combined injections but the geometric mean antibody levels for both were well in excess of protective levels.[99] Perhaps more importantly, a specific B-cell memory response was demonstrated in infants receiving the combination vaccine despite diminished antibody levels.[100]

2.4.4 Pentavalent and Hexavalent Vaccines

The additional combination of both Hib and hepatitis B vaccines with the SmithKline Beecham 3-component DTaP vaccine resulted in similar diminution in the Hib antibody response to that seen with tetravalent combinations (section 2.4.3);[101] the clinical significance of these findings in the presence of induced B-cell memory has not been established.[100] Similarly, diminished Hib antibody levels were demonstrated for the pentavalent combinations of the SmithKline Beecham 3-component DTaP, IPV and Hib[93] and the Pasteur-Mérieux-Connaught (France) 2-component DTaP, IPV and Hib.[94] Interestingly, however, the pentavalent acellular combination induced similar Hib antibody levels to a widely used pentavalent

Table IV. Summary of efficacy of acellular pertussis vaccines combined with diphtheria and tetanus toxoids in infants

Study site	Vaccine		Study methods		Percentage vaccine efficacy (95% confidence interval)	
	manufacturer	antigen(s)	study design	vaccination schedule (months)	acellular DTaP	whole cell DTwP
Stockholm[23]	Biken	PT	r,db	8,11	54 (26-72)	none
		PT/FHA	r,db	8,11	69 (47-82)	none
Goteborg[53]	Amvax	PT	r,db,pc	3,5,12	71 (63-78)	none
Senegal[59]	Pasteur-Mérieux-Connaught (France)	PT/FHA	r,db[a]	2,4,6	85 (66-93)	96 (86-99)
Munich[33]	Pasteur-Mérieux-Connaught-Biken (US)	PT/FHA	ccs	2,4,6	82 (68-90)	96 (78-99)
Mainz[68]	SmithKline Beecham	PT/FHA/PRN	b,hcs	3,4,5	89 (77-94)	98 (83-100)
Erlangen[47]	Wyeth-Lederle-Takeda	PT/FHA/FIM2	r,db[b]	3,4,5,6,15-19	83 (76-88)	93 (89-96)
Italy[69]	SmithKline Beecham	PT/FHA/PRN	r,db,pc	2,4,6	84 (76-89)	36 (14-52)
	Chiron	PT/FHA/PRN	r,db,pc	2,4,6	84 (76-90)	As above
Stockholm[70]	SmithKline Beecham	PT/FHA	r,db,pc	2,4,6	59 (51-66)	48 (37-58)
	Pasteur-Mérieux-Connaught-Biken (Canada)	PT/FHA/PRN/FIM 2&3	r,db,pc	2,4,6	85 (80-89)	As above

a Absolute efficacy measured in a nested household contact study.

b Nonrandomised open diptheria-tetanus control.

b = blinded; **ccs** = case control study; **db** = double-blind; **FHA** = filamentous haemagglutinin; **FIM** = fimbriae; **hcs** = household contact study; **pc** = placebo controlled; **PRN** = pertactin; **PT** = pertussis toxoid; **r** = randomised.

whole-cell pertussis combination.[102] No such diminution in the Hib antibody response was found with the Pasteur-Mérieux-Connaught (Canada) 5-component acellular pertussis vaccine combined with Hib and IPV.[103]

Efforts to manufacture a hexavalent vaccine (DTaP, Hib, IPV, hepatitis B) have also been hampered by diminished antibody responses, particularly to the Hib component.

3. Recommendations for Use

The most important factor in the control of pertussis is the widespread use of pertussis vaccine. This is now feasible, with the current availability of effective whole-cell and acellular pertussis vaccines. The increase in global coverage with whole-cell pertussis vaccines through the Expanded Program on Immunisation is now being complemented by higher immunisation rates against pertussis using acellular pertussis vaccine in countries that had previously discontinued immunisation with the whole-cell vaccine (such as Sweden) or where uptake with the whole-cell vaccine was low (such as Germany and Italy). The availability of a choice in vaccine products will now permit a renewed effort to increase pertussis vaccine utilisation.

The choice of vaccine for use by either public health authorities or by practitioners is complex; consideration must be given to a variety of factors including safety, immunogenicity, efficacy and cost. A choice must be made to use either the acellular or whole-cell pertussis vaccines and a specific vaccine product must also be chosen. Adverse events are important both from a safety perspective and in improving compliance and rates of vaccine uptake. The commonly reported local and systemic vaccine-associated adverse events (injection site erythema, swelling, tenderness, fever, irritability, crying) are less frequently reported after acellular pertussis vaccines than whole-cell pertussis vaccines. The frequency of rarer events, such as hypotonic-hyporesponsive episodes, is reported to occur with similar frequency[16] or less commonly[69] with acellular pertussis vaccine compared with the whole-cell vaccine. Immunogenicity of the vaccines is of more limited use in choosing a particular vaccine because all have been demonstrated to be immunogenic. Serological correlates of protection have been lacking in pertussis so the choice cannot be made on antibody levels alone, although recent analysis of two of the recent acellular pertussis vaccine efficacy studies suggest the importance of fimbriae, PRN and, to a lesser extent, PT antibodies, but not FHA antibodies, in protection.[104-106] Vaccine efficacy data are important in selecting a particular vaccine, although the assessment of the relative efficacy of acellular pertussis vaccines is fraught with difficulty because of differences in study design, populations and definitions. Efficacy criteria for the whole-cell pertussis vaccines are even more difficult to assess; there is an increasing awareness that all whole-cell pertussis vaccines are not the same and few products have actually been tested for efficacy in a clinical trial. Finally, in reality, cost may be a major limiting factor in whether a particular vaccine product is used. In developing nations, the whole-cell pertussis vaccine combinations are available for a fraction of the price of the acellular vaccines. For this reason, most developing nations have continued to use the whole-cell vaccines and will likely do so until the cost of the acellular products decreases. In some countries (such as Germany, Sweden and Canada), all pertussis immunisation is performed with the acellular pertussis vaccine. In the US, a preference is stated by the advisory committees for acellular pertussis vaccine although whole-cell pertussis vaccine is still offered as an alternative if acellular pertussis vaccine is not available.[23,107]

Whether there is an optimal composition of an acellular pertussis vaccine has sparked a great deal of debate. Controversy persists on whether pertussis toxoid alone is optimal as an immunising agent. Proponents point to proven efficacy of a monocomponent PT vaccine and suggest advantages in its simplicity and the theoretical benefits of decreasing antigen interactions and adverse events.[108,109] Other experts suggest that more complex multiantigen products are more effective and point to the results of the efficacy studies that included vac-

cines with different numbers of antigens in the same study.[16,110,111] Others claim that there are still insufficient data to make a determination.[112] The weight of the data from the efficacy studies performed to date would support the contention that the additional antigens present in acellular pertussis vaccines with 3 or more components do confer additional protective efficacy.[71,103,104,106]

The optimal schedule for the use of acellular pertussis vaccines has also not been established, nor has the need for or frequency of booster doses. A variety of schedules have been used for the first 3 doses including 2, 4 and 6 months, 3, 4 and 5 months, and 3, 5 and 12 months; all were demonstrated to be effective. Increased efficacy with a fourth dose was demonstrated in some trials although equivalent efficacy was demonstrated in other studies using only 3 doses. Although fifth doses of acellular pertussis vaccine are recommended in some areas, there are no data available yet to determine if this or additional doses are required.

Contraindications to the use of acellular pertussis vaccine vary with country/region. Product monographs for some acellular pertussis vaccines list identical contraindications as for the whole-cell pertussis vaccine. Some advisory bodies such as those in the US use similar contraindications for the acellular and whole-cell pertussis vaccines. In contrast, in Canada, the only contraindication for the use of acellular pertussis vaccine is anaphylaxis to a previous dose or to any vaccine constituent.

4. Future Directions

Although the availability of acellular pertussis vaccine has inaugurated a new era in the prevention of pertussis, there are many avenues for future research and development. The benefits of combination vaccines are well recognised[113,114] although there are limitations.[115] Efforts to produce combination vaccines with several components continue. Further assessment and confirmation of serological or other correlates of immunity will assist in the design of future vaccine products. A better understanding of the role of cellular immunity in protection against pertussis[116,117] will also assist in vaccine development. Further development of recombinant vaccine antigens may assist in standardising the vaccine content. Mucosally delivered vaccines are in the early stages of development and could serve to simplify vaccine delivery systems world wide.

In addition to these future directions in vaccine development, research is necessary to better define the optimal way to use acellular pertussis vaccines. The number and frequency of booster doses has not been established. The role of acellular pertussis vaccines for the control of pertussis in adolescents and adults is actively being studied.

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