Communicable Disease Intelligence

PERTUSSIS AND THE ACELLULAR VACCINES

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Abstract

Morbidity and mortality from pertussis continue to be a problem worldwide, both because the organism is difficult to eradicate and because there is non-compliance with vaccination, often owing to concerns about side effects of the whole-cell vaccine. The new acellular vaccines have fewer side effects and appear to be efficacious, although costly. Some have been approved in other countries for use in infants and children, but none is yet available in Australia. Once they are introduced, careful surveillance will be needed to monitor any epidemiological changes.

Pertussis and pertussis vaccines

It is 90 years since Bordetella pertussis was first isolated by Jules Bordet in Brussels in 1906. Simple vaccines containing a suspension of the whole organism were made soon afterwards, yet only last year the annual incidence of pertussis was estimated at 40 million cases, with around 360,000 deaths (B. Ivanoff and SE Robertson 1995, personnal communication). Most deaths occur in children, particularly infants. The burden falls most heavily on children in developing countries, in which case-fatality rates of up to 15% have been quoted.

Why is it taking us so long to control this disease? The first commercial vaccines were developed 60 years ago in the 1930s, and effective vaccines were widely used in the 1940s and 1950s. Although these whole-cell vaccines reduced the incidence of whooping cough and the associated morbidity and mortality, they did not provide absolute protection. However they ensured that pertussis in vaccinated children was a much milder condition. In Australia, the Commonwealth Serum Laboratories (CSL) first manufactured pertussis vaccine in about 1920, and in 1953 a more potent vaccine was incorporated with diphtheria and tetanus vaccines as Triple Antigen, with a resulting fall in prevalence and mortality. In Melbourne the case-fatality rate fell from 21% in 1919 to 0.1% in 1969[1].

Unfortunately, immunity following vaccination does not persist. The efficacy fell from 100% to 52% five years after vaccination in one study[2], so even in well-vaccinated communities there may be pools of susceptible adults, in whom pertussis can cause persistent cough[3]. Individuals with waning immunity, such as parents or health care workers, may develop attenuated or atypical attacks of pertussis and pass the infection on to infants, but there is no evidence of long-term asymptomatic carriage. Pertussis is highly infectious: the secondary attack rate in unimmunised household contacts is about 80%[1], and chemoprophylaxis with erythromycin cannot always be relied on to eradicate *B. pertussis* from the respiratory tract[4,5]. Erythromycin prophylaxis is useful when given before the onset of the first secondary case[6] but other children in the household are often infected by the time the disease is recognised in the index case. Its use also appeared to shorten the duration of coughs in patients in one non-randomised study[7].

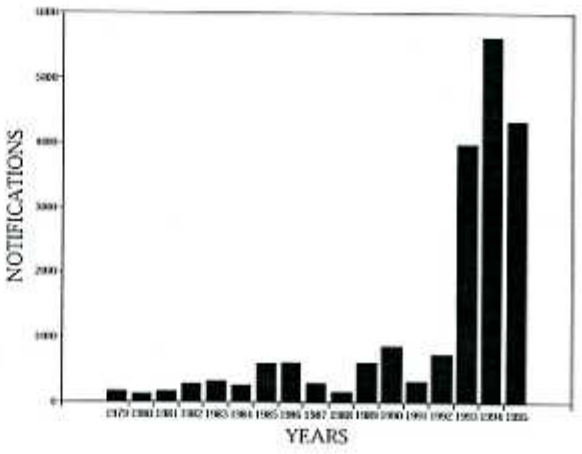
In the United Kingdom, the vaccine became available in the late 1940s, and the incidence of the disease declined in the 1950s following its widespread use. However a four-year cycle of epidemics peaking in autumn was still observable, even with a high uptake of vaccination. Four years is believed to be the time needed for the number of susceptible people to increase sufficiently to overcome the threshold for herd immunity[8]. In the mid-1970s, following adverse publicity about side effects, uptake fell from more than 80% to less than 40% of children. This was followed by several large outbreaks of whooping cough, the most recent of which occurred in 1993[9]. In Australia, pertussis has been epidemic since 1993 (Figure). There were 5,633 cases notified in 1994, and 4,336 in 1995[10], with increasing numbers of cases in older age groups.

Since the 1980s, there have been cyclical resurgences of pertussis in the United States of America[11]; in 1993, 6,335 cases were reported, the most in 26 years[12]. Analysis of this epidemic in Cincinnati showed that it occurred primarily among children who had been appropriately immunised, confirming the failure of whole-cell pertussis vaccine to give full protection against the disease.

Why would she adult most of cases are vaccinated too?

In Japan there was such concern about side effects that vaccination was suspended for a short period in 1975.

Figure. Notifications of pertussis, 1979 to 1995[1]



1. Data courtesy of CommunicableDiseases Network Australia New Zealand, National Notifiable Diseases Surveillance System, 1996.

Virtually ALL cases in Aus are fully vaccinated ie children.
deaths = too young to vaccinate
But NOT ONE WORD against the vaccine

This concern stimulated the development in Japan of the first acellular pertussis vaccines.

Pathogenesis and epidemiology

The organism attaches to the ciliated respiratory epithelium. Here it multiplies rapidly and produces pertussis toxin and other toxins (which cause various effects, including the characteristic lymphocytosis). The toxins damage cilia and destroy ciliated epithelial cells. It is uncertain whether the cough is due to a central toxic effect, local respiratory inflammation, or both. The organism rarely invades deeper tissues or causes bacteraemia. Complications include apnoea, dehydration, bronchitis, pneumonia, convulsions and later bronchiectasis.

The pharmacological effects mediated by the various toxins are preceded by attachment of the organism to the respiratory mucosa. Important here are:

- filamentous haemagglutinin (FHA), which is involved in adherence and which stimulates production of antibodies that protect against respiratory challenge with live organisms;
- pertactin (PRN, formerly called 69-kd protein) a non-fimbriated antigen, which also plays a role in attachment and stimulates antibody production; and
- the fimbrial agglutinogens (AGGs), surface antigens which stimulate agglutinating antibodies. There are three AGGs which infect humans (1, 2 and 3), giving rise to three serotypes – type 1,2,3; type 1,2; and type 1,3. DNA fingerprinting of the organism has recently revealed a large number of DNA types, but these do not correlate with the more widely studied serotypes[9].

It seems that serotype 1,2 predominates in unvaccinated communities. It was present in the early vaccines and was highly protective, but its use slowly led to the emergence of type 1,3 as the predominant serotype in many countries[13,14]. When uptake of immunisation declined in the United Kingdom in the 1970s, type 1,3 became less common again, suggesting that organisms bearing AGG2 have a colonising advantage in unvaccinated individuals. This effect continued in the United Kingdom until the 1980s. In Australia, a similar situation was evident in the serotypying studies carried out at Royal Alexandra Hospital for Children between 1981 and 1990. Type 1,2 was prevalent up to 1987, while type 1,3 predominated later in the decade (Maureen Gapes, personal communication).

In the early 1980s in Australia there was an increase in the number of culture-positive cases and in the proportion of these involving preschool-age groups compared with the 1970s when the highest proportion was in younger children. In 1984 the National Health and Medical Research Council (NHMRC) appointed a working party to investigate the increased number of cases and the Australia-wide change in age distribution. The working party concluded that the change in vaccination schedule from four to three doses of pertussis vaccine in 1978-79 had been partly responsible and recommended reintroduction of the fourth dose (implemented in 1985). It also found that batches of the vaccine (produced from 1978 to early 1980) had low potency and advised that this should be rectified. One study of a series of children presenting to hospital showed a vaccine efficacy of 67% after three doses of vaccine in patients aged 1-4 years, and no protection in children from the age of four years onward[15]. In 1984 aluminium adjuvant was added to the vaccine available in Australia. Following these changes, cases in vaccinated preschoolers became less common and by 1989 and 1990 serotype 1,3 again predominated in Sydney. Due to time constraints, serotyping of isolates has not been performed at Royal Alexandra Hospital for Children since 1990. Of interest is the fact that in Australia the incidence of pertussis peaks in summer months.

Pertussis vaccination

Whole-cell vaccine

Pertussis vaccination is now routine in most countries and is incorporated into the World Health Organization's Expanded Programme on Immunisation (EPI). Fine[8] has noted that, although the vaccine has been responsible for significantly reducing the disease incidence and the morbidity, the public's concern has now 'paradoxically' focused on the uncommon side effects of vaccination, rather than on the common complications of this increasingly rare disease.

Whole-cell vaccine is a brew containing whole organisms. It also contains variable but significant amounts of lipopolysaccharide endotoxin. This small amount of endotoxin probably plays a major role in causing the fever, local reactions, pain and crying which follow vaccination. A study by the Commonwealth Serum Laboratories (CSL) several years ago showed that an endotoxin-depleted whole-cell vaccine had a much lower incidence of side effects. None of the acellular vaccines contains this endotoxin. The side effects of Triple Antigen (DTP), which contains whole-cell pertussis vaccine, used in a recent Australian study are shown in Table 1[16]. A previous larger Australian study found that about 0.1% of infants had a convulsion and a further 0.1% had a hypotonic-hyporesponsive episode after DTP[17]. The rate of anaphylaxis is estimated at about 1 in 50,000 doses and of acute encephalopathy at 0-10.5 cases per million vaccinations.

Vaccine potency, efficacy and serotype

The World Health Organization (1979) recommends that whole-cell vaccine includes AGGs 1, 2 and 3, and for potency passes the mouse protection test, in which the degree of protection induced by the test vaccine is compared with that provided by a reference vaccine when the mice are challenged by intracerebral inoculation with the live organism[18]. Each dose should contain not less than four international units. However, to date there are no clear serological correlates with protection or efficacy. For example, although subjects vaccinated with acellular vaccines may have higher antibody lev-

Table 1. Side effects of Triple Antigen containing whole-cell pertussis vaccine (DTP) in 591 Australian children

Reaction	Percentage[1]
Systemic	
Fever ≥ 38°C[2]	16
Irritability	90
Crying - intermittent, inconsolable	40
Crying - persistent high-pitched	8
Vomiting	11
Hypotonic-hyporesponsive episode	0
Convulsions	0
Local	
Redness ≥ 2.4 cm	27
Induration ≥ 2.4 cm	30
Swelling	45
Tenderness	46

1. Mean after first three doses at two, four and six months of age, to the nearest whole number.
2. All children were given at least two doses of paracetamol around the time of each vaccination.

els, they cannot be said to be more or less likely to be protected than subjects vaccinated with whole-cell vaccines. There are no efficacy data published for the whole-cell vaccine currently marketed in Australia.

British workers have found that when whole-cell vaccine is used widely, the predominant serotype in the community changes from 1,2 to 1,3. They believe that acellular vaccines should be shown to be efficacious against both serotypes before being licensed for infants[19]. Some data on this are available from the German studies[20]. Vaccine efficacy is conventionally expressed as protection from disease, rather than as protection from infection. Fine and Clarkson[21] believe that there is evidence that whole-cell vaccine protects to a lesser extent against infection than against disease. This gives the organism the ability to continue to circulate in the community. However, Preston argues that the very low rates of disease in some Eastern European countries after many years of high compliance with whole-cell vaccination is against this hypothesis[22].

Acellular vaccines

Once the biologically active components of the organism had been identified, development of acellular pertussis vaccines became possible. Those which have been produced commercially contain inactivated concentrates from the culture fluid of the organism, and may contain one to five components which include FHA, one or two agglutinogens, pertactin and pertussis toxin. It is not certain which components are most correlated with protection from infection, but it is likely that both FHA and pertactin are important.

Acellular vaccines were licensed for use in Japan in 1981. Initially they were used only in two year old children; in 1988 they became available for infants. There has been a dramatic decline in the prevalence of the disease since their introduction. Protective efficacy has been high and reactogenicity low, and protection has been shown to last for up to ten years. However, in Sweden, which had ceased using its whole-cell vaccine in 1979 because of limited efficacy[23], the first trials of acellular vaccines did not confirm the high rate of protection seen in Japan. In 1985, an early trial of two acellular vaccines (a single-component (PT) vaccine and a two-component (PT & FHA) vaccine) showed efficacies of only 54% and 69% respectively[24].

In the 10 years since the Swedish studies, the vaccines have been further improved and subjected to a series of rigorous trials. Most now contain two to five pertussis antigens, together with aluminium and a preservative. They generate much higher antibody titres than the whole-cell vaccines; they also provoke levels of cellular immunity similar to those seen after natural infection. Importantly, they are associated with fewer and milder side effects than the whole-cell vaccine. In the large European trials, the frequency of side effects with the acellular vaccines was similar to the frequency after the control vaccine which contained only diphtheria and tetanus toxoids (DT) (Table 2)[25,26]. The rate of extremely rare adverse events such as encephalopathy after acellular vaccines is not yet known and will only be evident with careful post-marketing surveillance.

Because the question of efficacy was not resolved at the time, the United States in 1991 licensed acellular vaccines only for the fourth and fifth doses of the childhood immunisation schedule. Recent United States trials of 13 acellular vaccines in infants showed that they were associated with fewer and less severe adverse reactions than whole-cell vaccines[27,28]. The United States of America is currently proceeding to license a three-component acellular vaccine for use in infants, and Germany has already done so. The effects of this change will require close monitoring.

Efficacy studies of acellular vaccines

Even though the acellular vaccines had been shown to stimulate development of high levels of antibodies (that is, they were immunogenic), their ability to prevent clinical infection (their efficacy) still had to be demonstrated. Six National Institutes of Health-sponsored large-scale phase III efficacy trials, which included both a DT control group and a whole-cell comparison group, are now completed or near completion. Preliminary results of these randomised double-blind trials, involving 25,000 children in Europe, show clear evidence of efficacy (in Sweden 85% for a five-component vaccine (PT, FHA, pertactin, AGGs 1 and 2) and 59% for a bivalent vaccine (PT and FHA)[26]; and in Italy 84% for two 3-component vaccines (PT, FHA, pertactin)) and fewer side effects compared with the control group that received whole-cell pertussis vaccine[25,26,29]. According to Edwards and Decker[30], these results suggest that the presence of fimbrial pro-

Table 2. Side effects[1] of two 3-component acellular pertussis vaccines (DTaP) compared with whole-cell pertussis vaccine (DTP) and DT vaccine in 14,751 Italian infants[2]

Reaction	Percentage			
	Acellular vaccine 1 (13,761 doses)	Acellular vaccine 2 (13,713 doses)	Whole-cell vaccine (13,520 doses)	DT vaccine (4,540 doses)
Systemic				
Fever ≥ 38°C[3]	7.2	4.3	40.5	3.4
Crying - persistent ≥ 3 hours	0.04	0.07	0.4	-
Hypotonic hyporesponsive episode	-	0.007 (1 case)	0.07 (9 cases)	0.04 (2 cases)
Seizures (within 48 hours)	0.007 (1 case)	-	0.02 (3 cases)	-
Local				
Swelling	9	7	26	6
Tenderness	4.6	4.6	30	4.5

1. Within 48 hours of each of the first three doses.
2. Based on reference 25.
3. Rectal temperature.

teins in the five-component vaccine did not improve efficacy, but the presence of pertactin increased protection in the trivalent vaccine compared with the bivalent vaccine. In these studies, the whole-cell vaccine (a product licensed and manufactured in the United States of America and not available in Australia) showed efficacies of 36% in Italy and 48% in Sweden. Trials under other sponsors are also under way in Germany, Senegal and Sweden. One recent German study of a three-component vaccine given at ages three, four and five months showed an 88.7% efficacy in children exposed within their household to a case of pertussis, compared with 98% for a German whole-cell vaccine[31].

In most of these trials, the acellular pertussis vaccines were combined with diphtheria and tetanus toxoid, and the resulting combination (DTaP) was compared with the conventional DTP which contains whole-cell pertussis vaccine. Tetravalent and pentavalent vaccines, in which Haemophilus influenzae type B and hepatitis B vaccines are added to DTaP, have also been developed and tested. Such combinations are difficult to make with the acellular vaccines. They will reduce the number of immunisations required in infancy.

Eradication: is it possible?

On both practical and theoretical grounds, eradication seems unlikely in the immediate future. Infants who are too young to have completed their primary schedule need to be protected by herd immunity. Commencing vaccination in the neonatal period has not proved successful and the adoption of an accelerated infant schedule in Britain in June 1990 (doses given at two, three and four months) has not yet reduced the number of cases in children under the age of one year[14].

It is possible that some acellular vaccines may prove more efficacious than whole-cell vaccine and be more suitable for use as adult boosters. Future vaccines which enhance specific IgA production and are administered orally are being developed. So are synthetic peptide vaccines aimed at inducing an immune response which will block adhesion of the organism to the cell. But these are still to be evaluated in clinical trials and are likely to be a decade away.

Current situation in Australia

Not until a vaccine is licensed will the National Health and Medical Research Council decide whether acellular vaccines are to be recommended for use in the routine infant schedule in Australia. Their widespread use may depend on whether their appreciably higher cost will be publicly funded in the same way that other routine childhood vaccines now are. For the present, we must continue to use whole-cell DTP. Serious reactions to vaccination, which contraindicate further doses of whole-cell pertussis vaccine, including anaphylaxis and unexplained encephalopathy, are very rare[32]. Doctors should strongly discourage the inappropriate deferral of pertussis immunisation due to mild illness, and the omission of pertussis vaccine because of inappropriate contraindications.

Once the new acellular vaccines are licensed, they are likely to be more acceptable to parents, especially when they are included in combination with other antigens. They are also likely to be useful for boosting immunity in adults, perhaps combined with the ten-yearly boosters of adult diphtheria and tetanus.

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