

6 Pertussis (Whooping Cough)

6.1 Introduction

Descriptions of pertussis appeared relatively recently (in the 16th century) in comparison with other common infectious illnesses, such as mumps and measles. As the disease became widely known it was given different names. The Italians spoke of the ‘dog bark’, while in England it became known as the ‘chin cough’ or ‘kin cough’, later to be called whooping cough. The Chinese called it the ‘100 day cough’ because of the protracted course of the disease. Thomas Sydenham first used the term ‘infantum pertussis’ in 1670, ‘pertussis’ meaning a violent cough of any kind.

Bordet and Gengou identified the causative organism in 1906 (hence the name *Bordetella pertussis*), and the first crude vaccine was developed soon after from killed bacteria. An improved understanding of the organism resulted in a standardised whole cell vaccine. During the 1980s and 1990s knowledge of the components of *B. pertussis* and their biological roles led to the development of acellular pertussis vaccines.

Pertussis is unusual for an infection in that it produces higher morbidity and mortality in females than in males, which is more apparent with increasing age. The reason for this is unknown.

6.2 The illness

Pertussis is a highly infectious bacterial disease spread by droplets, with an incubation period of 7–10 days (range 6–20 days). A case is most infectious from seven days after exposure until three weeks after the onset of the typical paroxysms. As many as 90 percent of non-immune household contacts will acquire the disease. *B. pertussis* is a small, gram negative, pleomorphic bacillus. The bacillus is fastidious, hard to culture, and will often have cleared or decreased in numbers by the time the typical cough develops, making laboratory confirmation difficult.

The initial catarrhal stage, which is the most infectious period, is of insidious onset with rhinorrhoea and an irritating cough that can progress to severe paroxysms of coughing. In the catarrhal stage, which usually lasts one to two weeks, the only clue to diagnosis may be contact with a known case. This stage is followed by the paroxysmal stage, with paroxysms characterised by a series of short expiratory bursts, followed by an inspiratory gasp or typical whoop and/or vomiting. Not all children whoop. Whooping is unusual in adults and relatively uncommon in infants. Infants may develop apnoea between paroxysms. Patients appear relatively well between paroxysms and are commonly afebrile.

The most common complications of pertussis are secondary infections, such as otitis media and pneumonia, and the physical sequelae of paroxysmal coughing (eg, subconjunctival haemorrhages, petechiae, epistaxes, central nervous system

haemorrhages, pneumothoraces and herniae). At the peak of the paroxysmal phase vomiting can lead to weight loss, especially in infants and young children. Infection may be particularly severe in young infants, in whom prolonged periods of apnoea may result in cyanosis, anoxic encephalopathy, convulsions and death.

Only limited data is available on the risk of encephalopathy from pertussis, with estimates from early population based studies ranging from 0.008 to 0.08 percent of cases.¹ A review of notified cases of pertussis in the United States (US) between 1980 and 1989² found that 0.7 percent developed encephalopathy and 2.2 percent seizures. In contrast, 0.1 percent of cases reported in the US between 1992 and 1995 were complicated by encephalopathy. The lower rate may reflect an increased recognition of pertussis in adolescents and adults, who are less likely to have severe complications, or the more comprehensive reporting of milder, non-hospitalised cases.

Studies performed in Australia, Canada, France, Germany and the US during both epidemic and non-epidemic periods have shown that between 12 and 32 percent of adolescents and adults with persistent cough have evidence of recent *B. pertussis* infection.^{3,4,5,6,7} Infection frequently occurs in adults in households where there are other people with pertussis.⁸ Serological surveys also suggest that pertussis infection is a common occurrence during adult life.^{9,10}

6.3 Epidemiology

Pertussis mortality

Historically, pertussis mortality rates have always been higher in the first year of life than at any other age.¹¹ Beyond three years of age mortality rates have always been relatively low. The concentration of deaths in the first year of life, with markedly lower death rates in toddlers and preschool aged children, is different from the pattern seen with other acute childhood infectious diseases, where a larger proportion of deaths occur in children between one and five years of age. Mortality rates were and remain highest in the first few months of life. Young age, lack of immunisation, low socioeconomic status and premature delivery are associated with an increased risk of fatal pertussis.^{12,13,14,15}

Pertussis case fatality rates have decreased substantially over the past 100 years. For example, in the US the case fatality rate was 3.4 percent in 1930 compared with 0.2 percent in 1993.^{16,17} The case fatality rates in the US from 1992 to 1994 were 0.6 percent for children under six months of age, 0.3 percent for children between six and 11 months of age, less than 0.1 percent for children between one and four years and 0.2 percent for those five to nine years of age.¹⁸

Mortality due to pertussis, diphtheria and measles started to decline in industrialised countries prior to the introduction of mass immunisation, indicating that the initial decline in mortality was due to a reduction in the case fatality rate. In 1951 Gordon argued that the principal reason for the decline in the case fatality rate

was ‘an absolute and proportional reduction in physically substandard children’.¹⁹ This improvement in the general standard of health of children was due to a number of factors, including better nutrition, decreasing size of families and a decrease in birth rates during the Great Depression.

That immunisation made some contribution to the reduction in pertussis mortality was demonstrated in a review of the infant pertussis death rate in the US from 1900 to 1974. Had the decline in mortality from pertussis continued at the same rate as it was from 1900 to 1939, there would have been 8000 deaths from pertussis in the US between 1970 and 1974 rather than the 52 deaths that occurred.²⁰

However, pertussis deaths are under reported. It has been estimated that during the 1980s and 1990s the actual number of deaths from pertussis in the US and the United Kingdom (UK) was three to five times greater than the reported number of deaths.^{21,22,23}

Infants continue to die from pertussis. Death occurs despite state of the art intensive care.^{24,25,26,27} In the US the number of infant deaths from pertussis increased in the 1990s compared with the 1980s, mainly due to an increase in the number of deaths of infants less than four months old.²⁸

Pertussis morbidity

The majority of national epidemiological data on pertussis is collected via passive notification systems. Estimates of the proportion of pertussis cases that are notified vary between 6 percent and 25 percent. As well as underestimating disease incidence, passive notification systems are biased: a larger proportion of more clinically severe cases are notified and the proportion of cases that are notified decreases with increasing age.²⁹ The proportion of those hospitalised with pertussis who are notified has been estimated to be 23 percent.³⁰

Prior to mass immunisation, pertussis incidence was not decreasing. The introduction of mass immunisation was associated with a 5-to-100-fold reduction in pertussis incidence in Canada, England and Wales and the US between 1930 and 1980.^{31,32,33} Countries with consistently low pertussis incidence rates have had consistently high immunisation coverage rates (eg, Hungary and the former East Germany).^{34,35}

The higher incidence of pertussis in Canada compared with the US during the 1980s and 1990s was associated with the lower efficacy of the pertussis vaccine used in Canada.³⁶ Countries that have experienced large increases in pertussis incidence in association with reductions in vaccine coverage include the UK, Sweden and Japan.^{37,38,39,40,41}

The decrease in incidence following the introduction of mass immunisation has been most pronounced in those aged under 10 years. Despite this, the reported pertussis disease rates have remained highest in infants and young children.^{42,43,44} In the birth

to four years age group the majority of disease occurs in those under one year of age, and a large proportion of cases in these infants now occurs in the first three months of life.^{45,46}

The epidemiology of pertussis varies with age. Epidemic disease in young children occurs every three to four years, and the periodicity of these epidemics is unchanged by mass immunisation. Fully vaccinated individuals suffer less severe disease. Pertussis remains an endemic disease in adolescents and adults, with studies showing between 12 and 32 percent of adolescents and adults with persistent cough have evidence of recent *B. pertussis* infection (see section 6.2). This suggests that an adolescent and adult immunisation programme may decrease the circulation of *B. pertussis* in these age groups.⁴⁷

New Zealand epidemiology

Pertussis mortality in New Zealand

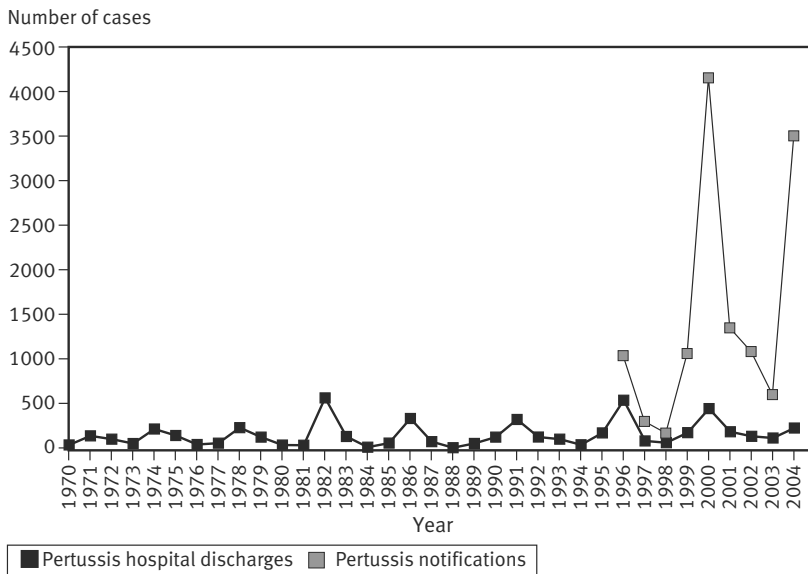
The estimated pertussis case fatality rate in New Zealand for the period 1970 to 1992 was 0.4 percent.⁴⁸ This is comparable to reported case fatality rates from the UK and the US over a similar period.^{49,50,51,52,53} There were no deaths from pertussis in New Zealand between 1988 and 1995, one death in 1996, and since 1999 there has been one death each year up to 2004.

Pertussis morbidity in New Zealand

Pertussis morbidity in New Zealand has been described primarily using hospital discharge data. National passive surveillance data has been available since 1996, when pertussis became a notifiable disease. Comparison of notification and hospitalisation data from 1996 and 1997 demonstrates that fewer than 50 percent of hospitalised cases are notified.⁵⁴

The three to four year periodicity of pertussis epidemics in New Zealand is similar to that seen in many other countries.⁵⁵ The pertussis hospital discharge and notification data are shown in Figure 6.1. It is apparent from this figure that the decrease in the pertussis hospitalisation rate that occurred following the introduction of mass immunisation has not been sustained.

Figure 6.1: Hospitalisations for pertussis 1970–2004, and notifications 1996–2004



National notification data was used to describe the epidemics in 1995–97, 1999–2001 and 2004/05. The rate of notified pertussis in 1996/97 was 19.8 per 100,000, and 82 percent of the cases notified were 15 months of age or older. In these epidemics the notification rate was highest in those less than one year of age.

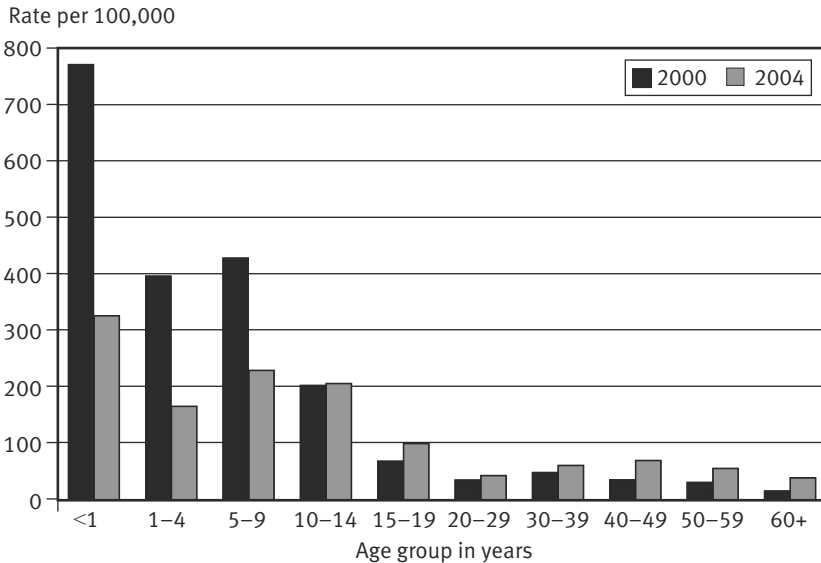
During the epidemic of pertussis from 1999 to 2001 there were 6523 cases notified to medical officers of health: 1046 cases notified in 1999, 4140 in 2000 and 1334 in 2001. The number of notified cases remained high in 2002, when 1068 cases were notified. In 2000, of the 4140 cases notified, 1979 (48 percent) were laboratory confirmed. The population rates for notified cases were 28.9 per 100,000 in 1999 and 114.6 per 100,000 in 2000. The rate was highest in infants under one year of age (773 per 100,000) in 2000, followed by children five to nine years of age (430 per 100,000) and children one to four years of age (398 per 100,000).⁵⁶

The most recent epidemic of pertussis started in April/May 2004 and continued into 2005. In 2004⁵⁷ there were 3489 cases of pertussis notified, a population rate of 93.4 cases per 100,000, and of these 1085 (31 percent) were laboratory confirmed. The highest rates of disease were reported from the South Island, except on the West Coast, and the rate was especially high in Southland, with a rate of 592 per 100,000. In the North Island, Waikato had high rates of disease. From the notification data in 2004, a total of 159 cases were hospitalised (3.4 percent).

The highest rates of disease were in infants less than one year of age, with a rate of 327.5 per 100,000, although rates were high up to age 19 years. There were also many cases reported in adults (see Figure 6.2 below). Among the notified cases, the population rates were higher in those of European ethnicity with a rate of 105 per 100,000, compared with 64 per 100,000 in Māori, 33 per 100,000 in Pacific peoples and 48 per 100,000 in those of ‘Other’ ethnicity. However, the highest rate of all groups was in Pacific infants under the age of one year, with a rate of 428 per 100,000. The hospitalisation rates were higher in Māori and Pacific infants during 2004.⁵⁸

An Auckland study of infants found that delayed immunisation in infancy is a risk factor for infants being hospitalised with pertussis.⁵⁹

Figure 6.2: Age specific rates of pertussis notifications during epidemics in 2000 and 2004



From Figure 6.2, although it is still too early to be sure, it does seem that the change of immunisation schedule in 2002 to include a dose at age four years has improved protection, and decreased disease in children age five to nine years in the current epidemic.

History of the New Zealand Immunisation Schedule

The monovalent pertussis vaccine was introduced by the Department of Health in 1945, and from 1953 was also available combined with the diphtheria vaccine. Routine childhood immunisation started in 1960, using the plain (ie, no adjuvant, not adsorbed) diphtheria tetanus and pertussis (DTwP) triple vaccine. Three doses were given at three, four and five months of age.

In 1971 the policy was altered to two doses of adsorbed triple vaccine given at three and five months of age. It was believed efficacy would be unaltered and the risk of serious reactions would be reduced. Following this schedule change there was a progressive increase in hospitalisations in 1974, 1978 and 1982. Review of the increase in hospitalisations led to the addition, in 1984, of a third dose of DTWP, given at six weeks of age, to provide earlier protection. The pertussis component used in New Zealand was a whole cell vaccine. From 1994 this was administered as a quadrivalent vaccine with diphtheria and tetanus toxoids and conjugate *Haemophilus influenzae* type b (DTwPH).

A fourth dose of pertussis vaccine was added in 1996 (as DTwPH vaccine) given at 15 months of age, with the goals of increasing protection in young children and reducing risk of transmission to younger siblings.⁶⁰

Acellular pertussis vaccine was introduced in August 2000, and diphtheria, tetanus and acellular pertussis (DTaP) and DTaP/Hib replaced the whole cell pertussis vaccines. In February 2002 the vaccine given at age six weeks, and at three and five months, was changed to DTaP with inactivated polio vaccine (DTaP-IPV), and a booster dose of DTaP-IPV was introduced and given at four years of age to protect children during the early school years and to decrease transmission of the infection to younger children.

In 2006 the timing of the pertussis schedule was changed so that, following the three doses of a pertussis containing vaccine in the first year of life, boosters will be given at ages four years and 11 years. The vaccine to be given at age 11 years is formulated with an adult dose of pertussis vaccine combined with tetanus, diphtheria and inactivated polio vaccine. This dose will improve protection in young adults. Note: A diphtheria, tetanus and pertussis vaccine is no longer administered at 15 months. Monovalent Hib and MMR vaccines are now given at age 15 months.

Immunisation coverage in New Zealand

The information available on immunisation coverage indicates that from the 1970s to the 1990s between 70 and 90 percent of children have received the complete series of the pertussis vaccine as prescribed by the National Immunisation Schedule. The 1991/92 national and the 1996 northern regional immunisation surveys indicated that 80–90 percent of children received the three dose primary series, but that only 50–60 percent of children completed the series within one month of the due date.^{61,62} A case control study performed in Auckland during the 1995–97 epidemic found that delay in receipt of any of the three infant doses of pertussis vaccine was associated with a five-fold increase in risk of hospitalisation with pertussis.⁶³ The analysis of the 2005 National Immunisation Coverage Survey shows that the overall immunisation coverage for the first three doses of pertussis vaccine during the first year of life is 89 percent, and that of these, only 52 percent received the third dose of DTaP-IPV on time, within four weeks of the due date (see also the Introduction). There has been only a small increase in immunisation coverage rates over the past 25 years.

Comparison of pertussis incidence rates and immunisation coverage rates from a number of countries demonstrates that immunisation coverage rates of 80–90 percent reduce pertussis notifications to a level approximately one tenth of that before pertussis immunisation was introduced. Immunisation coverage rates of approximately 95 percent reduce pertussis notifications to a level approximately one hundredth of that before pertussis immunisation was introduced.⁶⁴ For the burden of disease caused by *B. pertussis* infection in New Zealand to be decreased, immunisation coverage and on time immunisation need to increase significantly.

Reducing the size of future pertussis epidemics

The strategies to reduce the size of future pertussis epidemics include ensuring high immunisation coverage and on time immunisation, extending the duration of protection through either improved vaccines or a change in schedule, and offering pertussis vaccine to other population groups (eg, adolescents or adults). The current acellular pertussis vaccine used in New Zealand is around 84 percent effective (95 percent confidence interval [CI] 76–90 percent) in the first two years of life.⁶⁵ Subsequent surveillance of the original study population demonstrated sustained efficacy through to six years.⁶⁶

The goal of the current pertussis immunisation schedule is to reduce disease in those most vulnerable to severe disease; that is, infants in the first year of life. Even in countries with high immunisation coverage with pertussis vaccines, cases of pertussis continue to occur and the number and proportion of cases in young children appears to be increasing.^{67,68} As a result, there is growing interest in investigating how early effective immunisation may be started after birth, and whether, with the development and licensure of pertussis vaccines for adolescents and adults, pertussis disease can be reduced in adolescents and adults and thus reduce spread to vulnerable infants.

Early studies in neonates with whole cell pertussis vaccines had not shown benefit when given before one month of age.⁶⁹ However, a recent Italian study⁷⁰ using acellular pertussis vaccine given at age four days, followed by three, five and 11 months of age, found at age five months significantly higher proportions of the early vaccine recipients had a four-fold increase or more from baseline of anti-PT, (anti-pertussis toxoid) anti-FHA (anti-filamentous haemagglutinin) and anti-PRN (anti-pertactin) antibody levels compared with control infants. These findings need confirmation from larger studies before recommendations for earlier immunisation can be made.

In 2001 an International Consensus Group on Pertussis Immunisation⁷¹ looked at the role for the adult type acellular pertussis vaccine in preventing pertussis in adolescents and adults. The group reviewed studies on the disease burden of pertussis in all age groups and likely sources of infection. Adults in the household, unimmunised children, older children and health care workers were reported as sources of infection for young infants. There is limited information on the economic

benefits of adult pertussis booster vaccination. The group considered the aims of the vaccination programme to be to prevent clinical disease and to indirectly protect susceptible groups in the community. Although the ideal strategy was thought to be a booster programme for all adolescents and adults, it was considered unrealistic and a targeted approach was discussed.

Groups identified for targeted programmes included:

- adolescents in schools
- adults likely to come into contact with young infants, including parents, older children and health care workers
- new mothers after giving birth
- vulnerable adults and their close contacts whose health or age predisposes them to severe pertussis disease.

However, it was concluded that more research was needed on the incidence and natural history of pertussis in the population and on the immune response in women in the postpartum period, and that individual country decisions should be based on their own epidemiology.

If pertussis epidemiology is modelled mathematically⁷² it shows that even with three doses of pertussis vaccine in the first year, a dose in the second year of life and a booster at age four years, epidemics will continue to occur. The model shows that when pertussis vaccine is given at age 15 months and four years, the dose at 15 months adds little protection. This is because protection is expected to last six years, and is followed by gradual waning immunity. If the immunity is not boosted, either with vaccine or natural infection, the population gradually becomes increasingly susceptible to pertussis infection, and eventually an epidemic may be triggered. As can be seen from the cases reported in 2004, older children, many adolescents and adults developed pertussis, and they are known to pass the pertussis infection on to babies and infants.⁷³

A combination pertussis vaccine (see 6.4 below) has been registered for use in adolescents and adults in New Zealand. Pertussis vaccine given at age 11 years is expected to prevent outbreaks of pertussis in young adults.

The mathematical model for pertussis epidemics was run incorporating a dose of pertussis vaccine at age 11 years and dropping the dose at age 15 months. Overall population protection was somewhat improved. The mathematical model was also run simulating giving doses of pertussis vaccine to adults at age 45 and 65 years, when boosters of Td are due on the National Immunisation Schedule. The levels of protection expected in the community were improved, but because of waning immunity and gradually increasing numbers of susceptible children and adults, it was predicted that epidemics would continue to occur.

Modelling suggests that epidemics of pertussis would occur with the current vaccines even if boosters were given to adults at intervals of 10 years and coverage for all doses of pertussis vaccine was high. However, adult pertussis vaccine doses would reduce the potential reservoir of infection in the adult population. The effects of giving a birth dose of vaccine were modelled, but had little effect on the transmission of pertussis in the population. The focus for prevention and protection from pertussis must therefore continue to be on time immunisation and high coverage to all children, to protect infants as early as possible.

6.4 Vaccines

From 2006 the publicly funded acellular pertussis vaccine for the schedule is DTaP-IPV (INFANRIX™-IPV, GSK), a combination vaccine given at six weeks, three months and five months of age, and a fourth dose of DTaP-IPV at four years of age, prior to school entry. In addition, from 2006 a publicly funded combination vaccine of adult pertussis, diphtheria and tetanus, together with IPV, dTap-IPV (BOOSTRIX®-IPV, GSK), will be given at age 11 years (school year 7).

The INFANRIX™ contains diphtheria and tetanus toxoids and three purified *B. pertussis* antigens (pertussis toxoid – PT, filamentous haemagglutinin – FHA, and the 69 kilodalton outer membrane protein pertactin) adsorbed onto aluminium salts. The IPV content contains three poliovirus strains (see chapter 8: Poliomyelitis). The vaccine is formulated in saline and contains 2-phenoxyethanol as a preservative. INFANRIX™-IPV is presented as a turbid white suspension in a glass pre-filled syringe. On storage, a white deposit and clear supernatant are observed. The 0.5 mL dose contains not less than 30 IU of diphtheria toxoid, 40 IU of tetanus toxoid, 25 µg of PT, 25 µg of FHA and 8 µg of pertactin.

BOOSTRIX®-IPV contains not less than 2 IU of diphtheria toxoid, not less than 20 IU of tetanus toxoid, 8 µg of PT, 8 µg of FHA and 2.5 µg of pertactin, adsorbed into aluminium salts. The IPV content contains three poliovirus strains (see chapter 8: Poliomyelitis).

Other vaccines

Adult diphtheria, tetanus and acellular pertussis vaccine, dTap (BOOSTRIX™, GSK), is available for adult boosters but is not currently funded. Other acellular pertussis vaccines licensed for children in New Zealand include DTaP (TRIPACEL®, Aventis) and other combination vaccines, which include IPV, hepatitis B or Hib.

Efficacy of the acellular pertussis vaccine

The acellular pertussis vaccines licensed for use in New Zealand have been shown to provide 84 percent efficacy (95 percent CI 76–90), after three infant doses, with subsequent studies showing similar efficacy persisting to six years of age.^{74,75}

The reported efficacy in a trial of a monovalent acellular pertussis vaccine among adolescents and adults, aged 15 to 65 years, after a median of 22 months of follow

up, was reported as 92 percent (95 percent CI 32–99).⁷⁶ The case definition for primary pertussis in this trial was a laboratory confirmed case of pertussis with a history of cough illness of five or more days.

Dosage

The dose of DTaP-IPV and dTap-IPV is 0.5 mL, given by deep intramuscular injection. (See section 2.3 for needle sites and sizes.)

6.5 Recommended immunisation schedule

From February 2006 the recommended immunisation schedule is for the primary course of DTaP-IPV at six weeks, three months and five months of age. A booster dose is recommended at four years of age in the combination DTaP-IPV prior to school entry, to extend the duration of protection during the school years.

A further booster is given at age 11 years (school year 7) as dTap-IPV. The dTap-IPV vaccine will be given to children aged 11 years in 2006/07 because these children have not received four doses of polio vaccine. After this it is expected dTap will be given. The addition of pertussis antigen to the tetanus-diphtheria schedule at age 11 is expected to protect adolescents and young adults. If coverage is sufficient, this will reduce pertussis disease in this age group. IPV will continue to be given until the end of 2007, when all children would be expected to have received four doses of polio vaccine (see chapter 8).

Dose intervals for the primary series: the minimum interval between doses is four weeks, and the first dose should not be given before four weeks of age.

As at 2006, dTap and dTap-IPV are licensed for distribution for booster doses only. However, there are expected to be no safety concerns to giving three doses of dTap-IPV to previously unimmunised older children and adults. Therefore, using dTap should be considered for all catch up and adult schedules for primary and booster immunisation.

Dose intervals between Td and dTap-IPV

It is recommended that for students who have recently received a tetanus diphtheria (Td) vaccine booster, eg, at the time of an injury, the age 11 (year 7), dTap-IPV immunisation should be delayed until two years after the dose of Td, and offered before the student reaches the age of 16 years. Students who would normally receive the year 7 event at school should be referred to their general practitioner for follow up and recall.

Other recommendations

A booster of acellular pertussis containing vaccine is recommended, but not funded, for adults in the following occupations:

- health care workers working on paediatric wards, and in neonatal units
- adults in any occupation involving the care or education of infants and young children.

Recommendations for subsequent boosters will be made when further information is available.

6.6 Expected responses and adverse events following immunisation (AEFI)

Unless the specific contraindications and precautions outlined in section 6.7 are present, practitioners should have no hesitation in advising the administration of acellular pertussis vaccine. There is no convincing evidence that the pertussis vaccine can cause permanent neurological damage or disease (see section 20.2: f ii). Disorders for which any causal association with pertussis vaccine have been disproved include infantile spasms, hypsarrhythmia, Reye’s syndrome and sudden infant death syndrome (SIDS).^{77,78,79,80,81,82,83,84} The New Zealand Cot Death Study also found a lower rate of SIDS in immunised children.⁸⁵

Expected responses associated with pertussis vaccines

The acellular pertussis vaccines cause significantly fewer reactions than the previously used whole cell vaccines. Up to one third of infants will have redness at the site of the injection and 20 percent will develop a mild fever after a dose of acellular pertussis vaccine (see Table 6.1). As with the whole cell vaccine, the frequency of local reactions tends to increase with the number of doses administered.

Table 6.1: Percentage of mild to moderate reactions within 24 hours following a dose of acellular DTaP

Adverse reactions	Acellular vaccines*	
	Range	Average
Redness 1–20 mm	15.1–44.0	31.4
Redness > 20 mm	1.4–5.9	3.3
Oedema 1–20 mm	7.5–28.6	20.1
Oedema > 20 mm	0.8–8.0	4.2
Pain	1.6–13.2	6.9
Temperature 37.8°C–38.3°C	16.0–29.2	20.8
Temperature > 38.3°C	1.6–5.9	3.7
Irritation	12.0–24.4	17.1
Drowsiness	29.4–52.2	42.7
Loss of appetite	17.7–27.2	21.7
Vomiting	7.4–21.6	12.6

* There are 13 different acellular pertussis vaccines.

Sources: Edwards KM, Decker MD. 2004. Pertussis vaccine. In: SA Plotkin, WA Orenstein (eds). *Vaccines* (4th edition). Philadelphia: WB Saunders Company; Table 21-15 from Decker MM, Edwards KM, Steinhoff MC, et al. 1995. Comparison of 13 acellular pertussis vaccines: adverse reactions. *Pediatrics* 96: 557–66.

Update on expected responses following four or five doses of a DTaP containing vaccine

There is an increase in frequency of local reactions with increasing doses of a DTaP containing vaccine, although the number of reactions overall is not increased compared with a whole cell vaccine. Extensive limb swelling has been reported in some children following a fourth dose and/or a fifth dose of DTaP vaccine. The cause of this reaction is unknown but may be due to either or both the diphtheria or pertussis components of the vaccine. Pain is not usually prominent with this reaction and no treatment is necessary. Extensive limb swelling is defined as swelling extending from the injection site beyond one or both joints, or swelling of the entire proximal limb from joint to joint.

Children who suffer large swelling (over 50 mm) after a fourth dose of DTaP vaccine are more likely to have a reaction after the fifth dose,⁸⁶ but neither the large reaction nor extensive limb swelling is considered to be a contraindication to a subsequent dose. No treatment is necessary, but parents should be advised of the risk.

Studies on reactions after four or five doses of acellular pertussis vaccine

The rates of large swelling, defined as > 50 mm, following DTaP vaccine have been reported as varying between 1.6 and 10 percent after the fourth dose, and between 8.3 and 27.3 percent after the fifth dose of the same vaccine.⁸⁷ Of the children with entire thigh swelling, 60 percent had local pain and 60 percent had erythema. There were no differences in the proportion with fever when those children with entire limb swelling were compared with those without such swelling. In this study of 12 acellular vaccines and one whole cell vaccine, the rate of entire thigh swelling seemed to be correlated with the diphtheria toxoid content of the vaccine.

In a study from South Australia,⁸⁸ the rate of local reactions reported to the South Australia Immunisation Coordination Unit was 171 per 100,000 administered doses of DTaP vaccine after the fourth dose, compared with 12 per 100,000 reactions after the third dose. Practitioners were asked to report all severe and unexpected reactions, and details were collected on 45 of 71 infants reported with a reaction after the fourth dose of DTaP vaccine. After the fourth dose, swelling and redness occurred 0–72 hours post-injection (median 19.3 hours), and the swelling lasted for a median duration of 77 hours (range 24 to more than 168 hours), with complete recovery in all children reported by the author.⁸⁹ Eight (18 percent) of the 45 children followed up had extensive limb swelling, a rate of 19.3 per 100,000 administered doses.

Large limb swelling after immunisation was reported from the US Vaccine Adverse Event Reporting System in 2003. Reports to the system of whole limb swelling after immunisation from 1990 to 16 January 2003 were examined, over which time approximately two billion vaccine doses were distributed; 497 cases were identified, with 418 of these involving a single vaccine administered in the affected limb. Swelling involved the proximal limb, that is the area around the injection site in

67 percent, more than proximal limb in 16 percent and the whole limb in 17 percent. These reactions were reported in association with 23 different vaccine types in people ranging in age from 0.1 to 91 years. The most common vaccines with which limb swelling was reported were polyvalent pneumococcal vaccine, DTaP, Td, DTwP and influenza vaccine. Among patients seven years of age and under, entire limb swelling was more likely to occur after a higher number of doses of DTwP and DTaP. It was reported more commonly after the fourth (33 percent of 67 reports) and fifth (31 percent) doses of DTaP than after the first (10 percent), second (12 percent) or third (3 percent).⁹⁰

Adverse events associated with pertussis vaccines

The incidence of major adverse events following acellular pertussis vaccine (INFANRIX™) is summarised in Table 6.2 below.

Table 6.2: Incidence (per 100,000 doses) of major adverse reaction following acellular pertussis vaccine

Event following immunisation	Timing	Incidence per 100,000 doses
Persistent (> 3 hours) inconsolable screaming	0–24 hours	44
Seizures	0–2 days	7
Hypotonic, hyporesponsive episode (HHE)	0–24 hours	Nil in trial (7 to 26 per 100,000 in trials of other acellular vaccines)
Anaphylaxis	0–1 hour	Very rare

Source: Edwards KM, Decker MD. 2004. Pertussis vaccine. In: SA Plotkin, WA Orenstein (eds). *Vaccines* (4th edition). Philadelphia: WB Saunders Company.

Expected responses and adverse events after adult pertussis vaccine

An enhanced surveillance programme for vaccine associated adverse events was reported following a catch up dTap programme in 417 high school students in Yukon, Canada.⁹¹ The grade 12 students who took part in the study had received a dose of tetanus, diphtheria and inactivated polio vaccine in grade 9. It has been suggested that rates of local reactions increase with increasing number of doses of tetanus vaccine. In this study, the rate of reactions in students who had received their last dose of tetanus toxoid three to less than five years previously were compared with those in students who received the tetanus toxoid five or more years previously. Students who received the tetanus toxoid three to less than five years previously were more likely to report pain at the injection site than those who had received a dose five or more years before: 69 percent compared with 57 percent (Odds Ratio 1.72, 95 percent CI 0.96–3.1). Students who received tetanus toxoid three to five years before were less likely to report swelling at the injection site (3 percent compared with 13 percent), limitation of movement (27 percent compared with 47 percent), headaches (3 percent and 11 percent), body ache (1 percent and 9 percent), or sore joints (3 percent and 14 percent).

Severe events were defined as absence from school with symptoms related to vaccination, and one or more of the following: erythema or swelling > 46 mm, fever over 38.3°C and/or medical attention sought. Only 1 percent of those receiving toxoid three to less than five years ago had such a reaction, compared with 6 percent of those whose toxoid vaccination had been more than five years previously. The difference in rate of severe reactions between the two groups was not significant.

Evaluation of serious adverse events temporally associated with pertussis immunisation

All children who have a serious adverse event should be investigated with appropriate diagnostic tests to establish the cause. The adverse event may be unrelated to the vaccine. Any severe or unexpected reactions should be reported to CARM, PO Box 913, Dunedin, using the prepaid postcard HP3442 (see section 2.4) or via online reporting at <http://carm.otago.ac.nz>. If the patient or parent/caregiver does not consent to being identified, the report should be made without personal identification.

6.7 Contraindications and precautions

See section 1.9 for general contraindications for all vaccines.

Contraindications to pertussis vaccine have been overstated in the past. The only contraindication now accepted is severe reaction following a previous dose of pertussis vaccine (ie, immediate severe anaphylactic reaction to the vaccine, or any component of the vaccine), or an encephalopathy within seven days. Those with an evolving neurological disorder should not be immunised until stabilised (eg, uncontrolled epilepsy or deteriorating neurological state).

Before administering each dose of pertussis vaccine, the child's parent/caregiver should be asked about possible adverse events following the previous dose. Unless the child suffered a contraindication as above, the pertussis vaccine may be given.

Studies of reactions following pertussis vaccine

A small follow up study found that neither convulsions nor hypotonic, hyporesponsive episodes (HHE) were associated with long term consequences.⁹² Other follow up studies of children with HHE,⁹³ or convulsions following vaccination,^{94,95} have not identified any long term problems in these children when compared with children with febrile seizures not associated with vaccination. Children who have febrile seizures after pertussis immunisation do not have an increased risk of subsequent seizures or neurodevelopmental disability.⁹⁶ A Dutch study of 101 children with HHE after pertussis vaccination found that the 84 children who completed the course of pertussis vaccination did not have another HHE or other adverse event.⁹⁷ However, in another study, a child did have a second episode of HHE when given another dose of vaccine.⁹⁸ The safety of further pertussis immunisations after an HHE has also been shown in Australia.⁹⁹

When pertussis vaccine is genuinely contraindicated, DT, monovalent Hib and IPV vaccines should be offered instead.

6.8 Control measures

All cases of pertussis should be notified immediately on suspicion to the local medical officer of health. When the diagnosis of pertussis is suspected, all cases should have a laboratory test for confirmation of the diagnosis, as described below.

Consider the diagnosis of pertussis and the need for a nasopharyngeal swab in adults who present with a cough illness when there is a child under the age of one year living in the same household, particularly if the child is unimmunised.

Laboratory diagnosis of *Bordetella pertussis* infection

Pertussis can be diagnosed by direct detection of the *B. pertussis* in nasopharyngeal samples (a throat swab may be acceptable for testing although nasopharyngeal swab is preferable) by culture or PCR (polymerase chain reaction), or by serological methods. PCR is more sensitive than culture and is the preferred method for diagnosing pertussis early in the course of the illness.

Serology is particularly useful when symptoms have been present for several weeks, at a time when PCR and culture are likely to be negative. A variety of *B. pertussis* antibody tests are available, but only the detection of antibodies to pertussis toxin is specific for *B. pertussis* infection. Assays that detect antibodies to other antigens (eg, whole cell lysates) may be positive for infections due to other bacteria, such as *H. influenzae*.

Immunisation cannot be used to control an outbreak because a course of at least three doses of pertussis antigen (DTaP) may be required to induce protective immunity. However, individual immunisation status should be checked and immunisation completed. Infants as young as four weeks of age can commence immunisation.

A number of antibiotics are available for treatment and prophylaxis of pertussis. There are clinical trials to support the use of erythromycin, clarithromycin and azithromycin. Only erythromycin is fully funded in New Zealand, but it is associated with a wide range of side effects. Two weeks' therapy with erythromycin was originally recommended, but recent data suggests that one week of erythromycin estolate is as effective, and much better tolerated.¹⁰⁰ The newer macrolides probably have fewer gastrointestinal side effects. All antibiotics need to be started early, within 21 days of onset of cough, to have any appreciable impact on the duration of illness. Alternative antibiotics with *in vitro* or limited *in vivo* data to support their use include cotrimoxazole (960 mg bd for adults), roxithromycin, doxycycline and fluoroquinolones.¹⁰¹

Erythromycin has been shown to reduce the duration of time a person with pertussis is culture positive, but has not been shown to significantly alter the course of the

illness. There is some evidence that 14 days of oral erythromycin (40 to 50 mg/kg per day in divided doses, with a maximum of 2 g per day) may prevent pertussis from developing in close contacts (a seven-day course of erythromycin estolate may be used). Estolate may be more effective at eliminating carriage. There have been no studies of the effectiveness of seven days of erythromycin succinate therapy. In order to prevent the spread of pertussis in households, chemoprophylaxis with erythromycin must be started before a second person has started coughing and no later than 21 days after the first person with pertussis started coughing.^{102,103,104,105}

The antibiotic with the greatest clinical evidence is erythromycin in full dose for two weeks, although there is data supporting the use of azithromycin. An association has been reported between orally administered erythromycin and infantile hypertrophic pyloric stenosis (IHPS) in infants younger than two weeks of age. The risk of IHPS with other macrolides is unknown. Because the risk of severe illness in neonates is high, it is recommended that erythromycin continue to be used in neonates for the prophylaxis and treatment of pertussis.¹⁰⁶ Parents should be warned of the risk and signs of IHPS, and to report any concerns.

Those most at risk from pertussis are infants under one year of age. In households where a patient has pertussis and an infant less than one year of age resides, chemoprophylaxis should be offered to everyone in the household, especially if the infant has not received three doses of pertussis vaccine. This does not apply if the only infant in the household is the index case. Individuals in a household with a woman in the late stages of pregnancy should also be offered prophylaxis because of the risk of severe pertussis in the neonate. In early childhood services with infants under one year of age, prophylaxis may be considered for children who are in close contact, such as while sleeping at the centre.

Cases should be excluded from early childhood services, school, or community gatherings until:

- they are well enough to attend, and
- either they have received five days of antibiotics, or three weeks have elapsed since the onset of the coughing paroxysms (at which point they are unlikely to be infectious).

Children who have culture proven pertussis disease should complete their immunisation series with all of the scheduled doses recommended for their age. Inadequately immunised household contacts may be infectious during the prodromal stage of the illness and therefore should avoid contact with young children for up to two weeks following exposure. If household contacts receive a course of erythromycin, as described above, this period may be reduced to five days.

For more details on control measures, refer to *Control of Communicable Diseases Manual*.¹⁰⁷

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