The Epidemiology and Prevention of Pertussis in Australia

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Siranda Torvaldsen (BAppSci, GradDipEpi&Biostats, MAppEpid)

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Department of Paediatrics and Child Health

Abstract

Background

Pertussis (whooping cough) remains an important public health problem in Australia. Although mortality and morbidity from pertussis declined dramatically following the introduction of mass vaccination programs in 1953, the level of morbidity remains unacceptably high for a vaccine-preventable disease.

Aims and methods

The primary aims of this thesis were (i) to ascertain the epidemiology of pertussis in Australia between 1993 and 2000 by analysing and interpreting sources of routinely collected data on pertussis; and (ii) to examine the effectiveness of vaccination against pertussis in a number of ways. Data from three primary national sources (notifications of disease, hospitalisations for pertussis and death certificates) were used to examine the burden from pertussis in Australia over these eight years. Analyses included the age distribution of cases, temporal and geographic trends, comparisons of notification and hospitalisation data, and the impact of differences in the method of diagnosis of notified cases between years and age groups. In addition to analyses at the national level using data from the national databases, further detailed analyses were undertaken at the State level for New South Wales (NSW), the most populous Australian State.

Pertussis vaccine coverage was estimated using data from the recently established Australian Childhood Immunisation Register (ACIR); these data were also used to track the transition from whole-cell to acellular pertussis vaccines.

The different types of studies used to evaluate vaccine effectiveness were reviewed, and a method suitable for ongoing estimation of vaccine effectiveness in Australia was developed. This was then applied to the NSW data, to determine the effectiveness of pertussis vaccination in this State.

Main findings

The annual notification rate for pertussis in Australia ranged from 23–59 per 100 000 population over the eight years. Infants had the highest notification and hospitalisation rates in Australia — they accounted for 5% of notifications, 61% of hospitalisations and 100% of deaths. Age-specific notification and hospitalisation rates in children aged less than two years strongly suggested a protective effect of vaccination, with the greatest reduction in rate coinciding with eligibility to receive a second dose of pertussis vaccine at four months of age. Notification rates among 5–9 year olds progressively decreased in successive age cohorts, consistent with an effect of the introduction in 1994 of a pertussis vaccine booster for preschool-aged children. Although adults (persons aged 15 years or more) accounted for half the notifications, they had the lowest notification rate.

The highest numbers of pertussis notifications were in 1997, when most jurisdictions experienced an epidemic. Notification and hospitalisation rates varied across the States and Territories and also across smaller geographic regions in NSW. Areas and years with high notification rates tended to also have high hospitalisation rates, suggesting that trends in notifications reflected trends in incidence. The number of infant hospitalisations in NSW between July 1993 and June 1999 exceeded the number of notifications by 32%, highlighting the extent of under-notification.

Overall, and particularly amongst those aged more than 12 months, the majority of cases notified in NSW were based on the results of serological tests. The proportion diagnosed by culture of the organism was greatest in infants; the proportion diagnosed by serological tests increased with age. There was no evidence that the use of serology had increased since 1994 in NSW, hence changes in notification rates after this time are unlikely to be attributable to increased use of serological diagnosis.

ACIR records indicated that in December 2000, 92% of one-year-old children had received three doses of diphtheria-tetanus-pertussis (DTP) vaccine and 90% of two-year-olds had received four doses. Vaccine coverage varied by jurisdiction. Since 1997, there was an increased use of DTP vaccines containing acellular pertussis components with a corresponding decrease in the use of vaccines containing whole-

cell components. In 2000, almost all DTP vaccines administered contained acellular pertussis components.

The results of the vaccine effectiveness study showed that pertussis vaccination was highly effective at preventing pertussis in NSW children, as measured by notified cases. Vaccine effectiveness was highest (91%) in the youngest age group (8–23 months) and lowest (78%) in the oldest age group (9–13 years). The screening method has not previously been used to estimate pertussis vaccine effectiveness in Australia.

Conclusions

This thesis demonstrates the value of integrating varied data sources in estimating the disease burden from pertussis. The data presented here show that the disease burden is substantial in all age groups, despite high levels of vaccine coverage in infants and children. This problem of disease control does not appear to be due to lack of vaccine effectiveness, but there is evidence of waning immunity over time.

The analyses presented here form a basis for the ongoing monitoring of trends in pertussis epidemiology following the replacement of whole-cell by acellular pertussis vaccines, and will assist consideration of the need for additional booster doses in adolescents and adults.

Acknowledgments

Abbreviations used in this thesis

ABS	Australian Bureau of Statistics
ACIR	Australian Childhood Immunisation Register
ACT	Australian Capital Territory
AIHW	Australian Institute of Health and Welfare
ARU	attack rate in unvaccinated (cases)
ARV	attack rate in vaccinated (cases)
CDT	combined diphtheria-tetanus (vaccine)
CI	confidence interval
CSL	Commonwealth Serum Laboratories
CV	cases vaccinated
df	degrees of freedom
DTP	diphtheria-tetanus-pertussis (vaccine)
DTPa	diphtheria-tetanus-acellular pertussis (vaccine)
dTpa	diphtheria-tetanus-acellular pertussis (vaccine — the lower case letters indicate a reduced dose for adults compared with child formulations
DTPw	diphtheria-tetanus-whole-cell pertussis (vaccine)
ELISA	enzyme-linked immunosorbent assay
GPII	General Practitioners Immunisation Incentives
HOIST	Health Outcomes and Information Statistical Toolkit
ICD	International Classification of Disease
ISCOS	Inpatient Statistics Collection Online System
LOS	length of stay
NCIRS	National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases
NDD	Notifiable Diseases Database (NSW)
NHMRC	National Health and Medical Research Council
NNDSS	National Notifiable Diseases Surveillance System
NSW	New South Wales
PCR	polymerase chain reaction
PCV	proportion of cases vaccinated
PD	principal diagnosis
PPV	proportion of the population vaccinated
VE	vaccine effectiveness
VIVAS	Vaccine Information and Vaccine Administration Service
WHO	World Health Organization

Author's contribution

I am solely responsible for the design, analysis and interpretation of all the studies presented in this thesis. The following information sources were used: ABS Causes of Death Collection, ACIR, AIHW, NNDSS, NDD and ISCOS. I had some assistance with data extraction: Heather Gidding extracted the national pertussis notifications from NNDSS, Janaki Amin extracted national pertussis hospitalisation data from the AIHW National Hospital Morbidity Database, Micheline Hanna extracted NSW hospitalisation data from ISCOS and Brynley Hull extracted the relevant vaccination data from the ACIR.

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Chapter 1

Introduction

The disease

Pertussis (whooping cough) is a bacterial illness involving the respiratory tract. It is usually caused by the bacterium *Bordetella pertussis* but is occasionally caused by *Bordetella parapertussis*.[1,2] The illness generally begins with an irritating cough that gradually becomes paroxysmal and lasts for 1–2 months or longer. Paroxysms are characterised by repeated violent coughs which may be followed by a characteristic crowing or high-pitched inspiratory whoop and vomiting. Infants aged less than 6 months, adolescents and adults often do not have the paroxysms or whoop.[3] Pertussis is highly infectious, spreading via respiratory droplets to about 80% of unvaccinated household contacts.[4] With current standards of medical care in developed countries, mortality from pertussis is estimated to be 0.3% overall, but it is higher (0.5%) in infants aged less than six months.[5] Complications include hypoxic encephalopathy, which may result in brain damage and death.[5] Although antibiotic therapy given during the incubation or early catarrhal stage may prevent or modify clinical disease, treatment initiated after the onset of the paroxysmal cough does not affect the duration or severity of the clinical illness.[6] Complete vaccination of all children is the most important preventive measure for the control of pertussis.[7]

Vaccines

In Australia, the Commonwealth Serum Laboratories (CSL) began manufacturing whole-cell pertussis vaccine in 1920.[8] However, mass vaccination programs did not commence until 1942.[8] A more potent vaccine was licensed in 1953 which incorporated pertussis into the 'triple antigen' vaccine, together with tetanus and diphtheria toxoids.[4] This diphtheria-tetanus-pertussis vaccine is also known as DTP. At the same time as this vaccine was licensed, the three-dose schedule of DTP for infants commenced, although the timing of doses varied by State/Territory.[8] A national vaccination schedule was introduced in 1975, which recommended vaccination with DTP for infants at 3, 4, and 5 months of age, plus a booster dose at 15–18 months.[8] The booster dose was subsequently removed from the schedule in 1978, following a case-series in the United Kingdom which suggested a temporal association between the vaccine and brain damage in infants.[8] In 1982, the national schedule was changed to recommend vaccination with DTP for infants at two, four

and six months of age and vaccination with combined diphtheria-tetanus (CDT) for children at 18 months and prior to school entry.[8]

In the early 1980s there was a marked increase in the number of laboratory confirmed cases of pertussis and also an increase in the proportion of notifications involving preschool age groups, compared with the 1970s when the highest proportion was in younger children.[9] A working party, appointed by the National Health and Medical Research Council (NHMRC) to investigate this trend, concluded that the alteration in vaccination schedule from four to three doses of pertussis vaccine in 1978 had been partly responsible.[9] As a result of this finding, in 1985 a fourth dose at 18 months of age was re-introduced.[9] The working party also found that batches of the vaccine produced from 1978 to early 1980 were of low potency; this problem was rectified in 1984 by the addition of an aluminium adjuvant.[9] In the fifth edition of *The Australian Immunisation Procedures Handbook*, first published in October 1994, a fifth dose of DTP for children 4–5 years of age was added to the schedule to replace CDT.[10] In the seventh edition of the *Handbook*, first published in March 2000, the recommended age for the fifth dose of DTP was changed from 4–5 years to four years.[5]

Estimates of the efficacy of whole-cell pertussis vaccine vary considerably.[11,12] Efficacy estimates of whole-cell vaccines following three doses range from as low as 36% for the Connaught vaccine tested in Italy[12,13] to between 86% and 98% for Behring, Aventis Pasteur and Wyeth-Lederle vaccines tested in Germany and Senegal.[12,14] The effectiveness of the whole-cell pertussis vaccine used in Australia has not been tested.[15] Studies indicate that, although vaccination does not always provide absolute protection against pertussis, when vaccinated children have become infected with pertussis the ensuing disease has generally been milder and associated with fewer complications than in unvaccinated children.[9,16] Unfortunately, vaccination does not confer long-term immunity.[17] So even in well vaccinated communities there may be pools of individuals with waning immunity, such as parents or health care workers, who may develop milder or atypical episodes of pertussis and pass the infection on to infants.

In the past, non-compliance with pertussis vaccination was often thought to be due to concerns about the side effects of whole-cell vaccines. As a result, acellular vaccines have been developed. These new acellular vaccines have fewer side effects[18] and appear to be efficacious,[19] although they are more costly than the whole-cell vaccines.[9,20] GlaxoSmithKline's Infanrix,™ a three-component acellular pertussis vaccine combined with diphtheria and tetanus toxoids (DTPa), was licensed for use in Australia in 1997. The Commonwealth Government initially funded acellular vaccines in the national immunisation program for the fourth (18 month) and fifth (preschool) boosters, but since 1999 has also funded acellular vaccines to replace whole-cell vaccines in the primary vaccination course. Exceptions to this were South Australia and the Northern Territory, where the State and Territory governments funded DTPa for all doses in 1997. The efficacy of this vaccine was calculated to be 84% in a randomised controlled trial conducted in Italy in 1993[13] and 89% in a household-contact study undertaken in Germany in 1994.[14] Infanrix™ is also available combined with the hepatitis B vaccine as Infanrix-hepB.™ The only other DTPa vaccine licensed for use in Australia is Tripacel,™ manufactured by Aventis Pasteur Connaught and distributed by CSL.

Burden of disease

Pertussis is a major cause of morbidity and mortality in infants throughout the world. The true incidence of pertussis cannot be directly measured and estimates are generally based on data sources such as deaths, hospitalisations, notifications or studies designed for this purpose. The World Health Organization (WHO) estimates that there are 200 000–300 000 deaths and 20–40 million infections from pertussis each year.[21]

In Australia, after a prolonged period of apparent low pertussis activity following the introduction of mass vaccination programs, there appears to have been a resurgence of disease since 1993.[7] For the years in which data are available (national compilation of pertussis notifications ceased in 1949 and did not recommence until 1979[22]), the low notification rate in the post-vaccination years is evident (*Figure 1.1*). Similarly, the number of deaths Australia-wide each year due to pertussis decreased dramatically after the introduction of vaccination programs (*Figure 1.2*). However, from late 1996

to 1997 pertussis was responsible for ten infant deaths. One State, South Australia, did not discontinue pertussis surveillance and is the only source of continuous notification data since 1917.[23] The dramatic reduction in South Australian mortality and notification rates following the introduction of a mass vaccination program in 1953 is striking (*Figure 1.3*).[23] However, since 1993 notification rates have risen again.[23]

Figure 1.1. Annual adjusted pertussis notification rate, Australia, 1917–2000
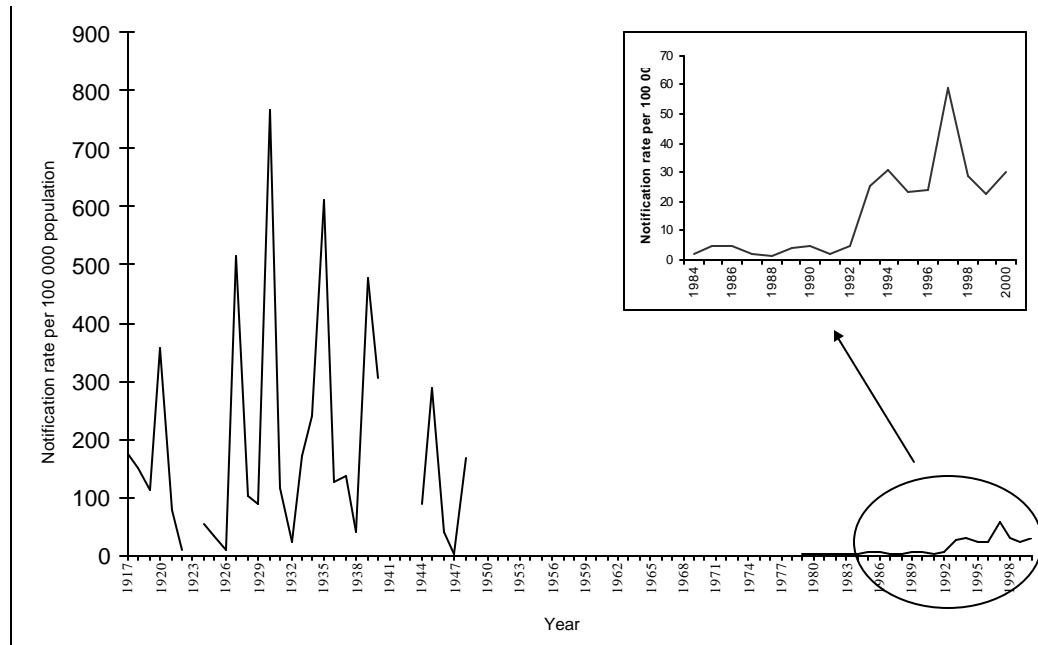
Source: Hall.[22] Rates were adjusted to estimate a national rate for the years when data were not available from all States and Territories. This was done by defining the denominator populations at risk as the total populations of those States and Territories where the disease was notifiable. The original graph has been updated with notification data from 1992–2000.

Figure 1.2. Deaths due to pertussis, Australia, 1907–1997
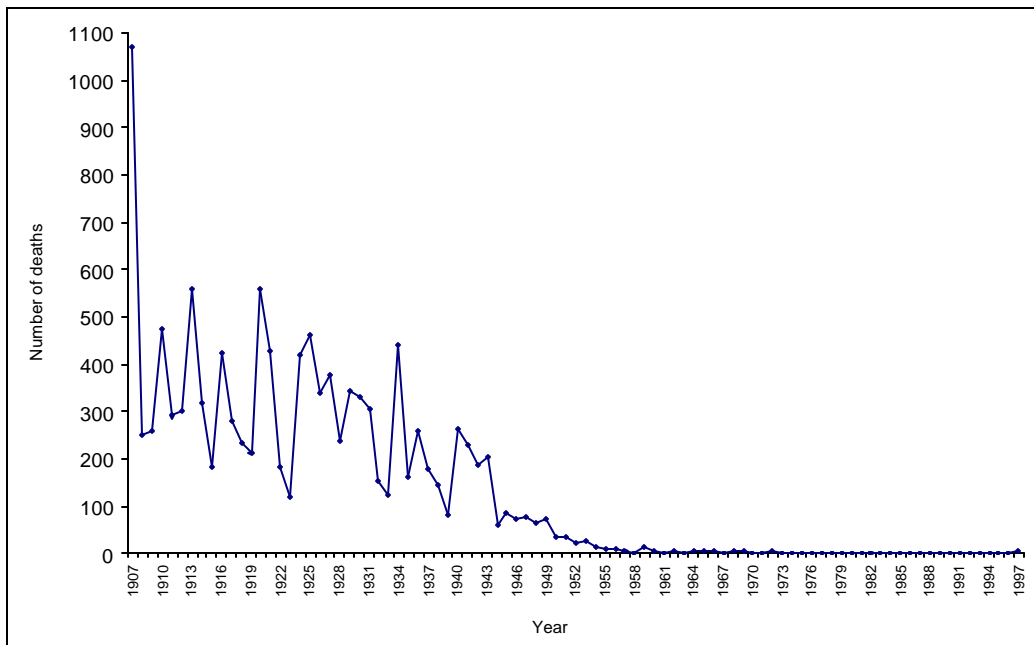
Source: Australian Bureau of Statistics, Causes of Death Collection.[24]

Figure 1.3. Pertussis crude death rate, 1893–1996, and notification rate, 1917–1996,
South Australia
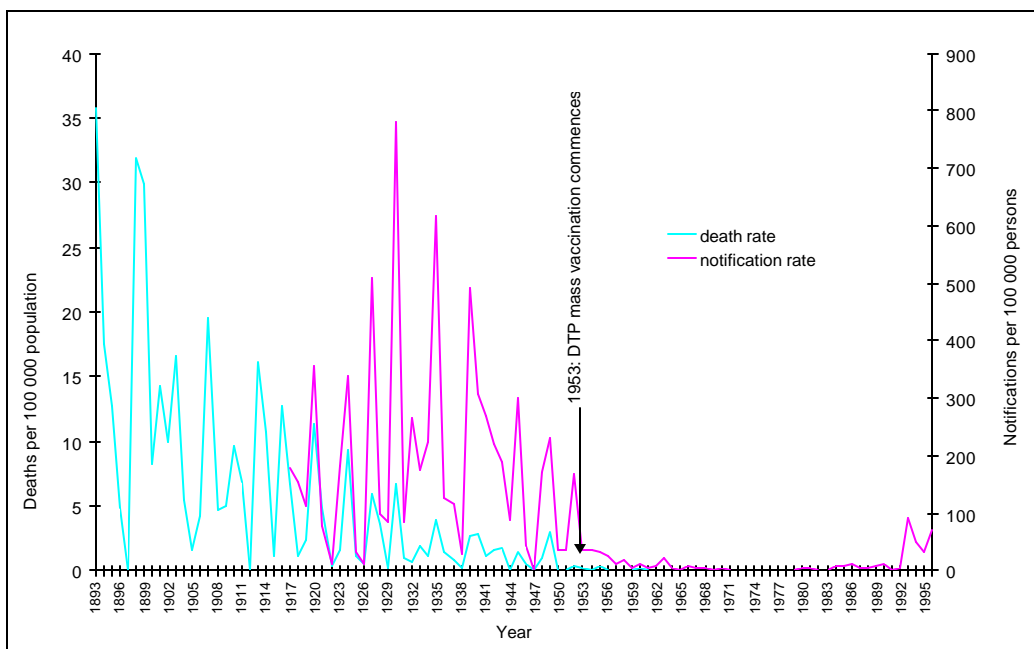
Figure reproduced from Scheil et al.[23]

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In both the mortality and notification graphs, peaks can be seen every three to five years prior to the introduction of mass vaccination programs (*Figures 1–3*). This cyclic pattern has been documented elsewhere and reflects the time needed for the number of susceptible people in a population to increase sufficiently to overcome the threshold for herd immunity.[25] This time period may vary and is dependent upon such factors as the birth rate, the population and vaccination. Even with high vaccine uptake rates, epidemics may still occur every three to four years, but these outbreaks are much smaller and have greatly reduced associated morbidity and mortality.[15,26]

Similar patterns in disease have been noted overseas with the introduction of vaccination programs. In the United Kingdom, an inverse correlation between pertussis incidence and pertussis vaccine uptake rates in different parts of the country were observable once pertussis vaccine was widely available in 1940.[26] However, pertussis vaccine uptake in the United Kingdom decreased in the mid 1970s from over 80% to less than 40% of all children, following adverse publicity about possible side effects of the vaccine.[9] Following this decline in vaccine uptake there was a dramatic increase in the number of notifications.[26] By 1993 public confidence in the vaccine had been restored and the vaccine uptake was estimated to be 93%.[26] As vaccine coverage increased, pertussis notifications fell dramatically, from 65 810 during the epidemic year of 1982 to 3963 cases during the epidemic year of 1994.[27] Similarly in Sweden, pertussis incidence in infants rose to pre-vaccination levels within four years of the withdrawal of locally produced pertussis vaccines in 1979.[28]

Pertussis vaccine coverage in Australia did not decline as it did in the United Kingdom and Sweden, and it was not until 1993 that notifications began to rise. In 1997, the Australian crude notification rates were reported as being ten times higher than those of the United States of America and three times those of England and Wales, in spite of similar levels of vaccine coverage.[29] In addition, there were differences in the age distribution of notified cases compared with the United States and Italy.[29] It was not clear whether these differences reflected variations in case definitions/ascertainment or true differences which could in turn be attributable to differences in vaccine coverage or the effectiveness of the vaccination program.

What this thesis contributes

While morbidity and mortality from pertussis have dramatically declined since the pre-vaccine era, the level of morbidity and mortality from pertussis remain unacceptably high for a vaccine-preventable disease. In order to reduce morbidity from pertussis we need to improve our knowledge and understanding of its epidemiology. In the guidelines for the control of pertussis in Australia, the Pertussis Working Party identified several areas in which research was needed.[7] This thesis addresses some of these issues as well as others which will improve understanding of the current epidemiology and control of pertussis in Australia.

Although routinely collected data have limitations, they are grossly under-utilised and can provide valuable insights into the epidemiology of pertussis, especially when two or more data sources are examined concurrently. In Chapter 2, *Pertussis in Australia: notifications, hospitalisations and deaths*, I bring together the most recent routinely collected national data available on the morbidity and mortality of pertussis — notifications to public health authorities, hospital discharge diagnosis data and death certificate data. Analyses include examination of the age distribution of pertussis cases, particularly among five to ten year olds, to assess the impact of the introduction of the fifth dose of vaccine, and assessment of geographic and temporal trends. Measuring the consistency in the magnitude and direction of notification and hospitalisation trends, particularly among infants who have high hospitalisation rates, can provide insights into the reliability of the data. An earlier draft of this chapter was included in *Vaccine preventable diseases and vaccination coverage in Australia, 1993-1998*,[30] which was published as an 84-page supplement to *Communicable Diseases Intelligence.*

Data collected at the State level in New South Wales (the most populous Australian State, accounting for 34% of the Australian population) are more comprehensive than the national data presented in Chapter 2. In Chapter 3, *Pertussis notifications and hospitalisations in New South Wales*, I provide more detailed analyses and interpretation of the New South Wales data than was possible using those reported to the national database. Additional data fields in the New South Wales Notifiable Diseases Database include exact age, method of diagnosis, the number of doses of

pertussis-containing vaccine received, whether the case was hospitalised and health area of residence. The New South Wales hospitalisation data include age in months and health area of residence, neither of which was available from the national hospitalisation data.

Information on the method by which notified pertussis cases are diagnosed is essential for the interpretation of trends in notifications over time and also for making international comparisons. It has been suggested that the increase in notifications could represent increased use of serological testing rather than an increase in pertussis incidence.[23] In Chapter 3, my analyses of the method of diagnosis of pertussis and differences over time and between age groups are presented.

Infants suffer the greatest morbidity from pertussis. Therefore it is important to examine the exact age at which infants are most at risk of disease onset and/or hospitalisation with pertussis. These analyses have not been previously undertaken and the results provide useful information about the impact of infant vaccination. A comparison of pertussis infant notifications and hospitalisations highlights the extent of under-reporting and how this varies by geographic region.

The vaccination status of cases is necessary to calculate vaccine effectiveness, a concept further developed in later chapters. The demonstrated utility of the additional information collected at a State level in New South Wales should encourage the collation of this information at a national level.

The examination of trends in uptake of pertussis vaccine (coverage) at a population level is essential for the interpretation of pertussis notification and hospitalisation data, and also for the estimation of vaccine effectiveness using the method described in Chapter 6. The Australian Childhood Immunisation Register (ACIR) is a national population-based register which commenced operation in 1996. In Chapter 4, *The Australian Childhood Immunisation Register and pertussis vaccination*, the background to the development of the ACIR is provided, followed by a presentation of pertussis vaccine coverage data from the ACIR, at both a national level and a State level for New South Wales. The New South Wales vaccine coverage data are

examined by month of age and health area of residence to determine the most appropriate coverage figures to be used later in the vaccine effectiveness estimations (Chapter 6). Data from the ACIR are also examined to track the uptake of the new acellular pertussis vaccines. From these analyses we can conclude that very few, if any, acellular vaccines were administered to cases included in the vaccine effectiveness study.

Chapter 5, *Observational methods in epidemiologic assessment of vaccine effectiveness*, provides a comprehensive review of the different studies which can be used to evaluate vaccine effectiveness. Observational methods are important in the measurement of vaccine effectiveness as experimental designs cannot be used for vaccines already on the vaccination schedule. Furthermore, efficacy measured in clinical trials under ideal conditions may differ from effectiveness in the field under non-ideal conditions and in different populations. Of the five observational study types reviewed (cohort studies, household contact studies, case-control studies, the screening method and case-cohort studies), the screening method is the cheapest and most rapid method.

The only other comprehensive reviews on this topic were published over 12 years ago. Many changes to the vaccination schedule have been made since then, including the introduction of new vaccines. This has increased the need for repeatable methods to monitor vaccine effectiveness in a timely fashion. This review includes references to practical examples and attempts to identify all observational studies of vaccine effectiveness in Australia and New Zealand since 1987. A shorter version of this chapter has been submitted to *European Journal of Epidemiology*.

Estimates of the effectiveness of pertussis vaccination in Australia was one of the key deficits identified by the Pertussis Working Party in 1997.[7] In Chapter 6, *Effectiveness of pertussis vaccination in New South Wales children*, I develop a method suitable for ongoing estimation of vaccine effectiveness. I then apply this method using data from New South Wales, collected during a period when the Australian whole-cell pertussis vaccine was in routine use, to estimate the effectiveness of pertussis vaccination in children aged less than 14 years. Vaccine effectiveness is calculated using the

screening method in a logistic regression model which includes age group, year of disease onset and area of residence as potential confounding variables.

This chapter has two parts. Part A uses notification data from 1993–1998. Due to limitations in the accuracy of vaccine coverage data from 1993–1995, more restricted analyses (using data from the years 1996–1998) were subsequently undertaken and are presented in Part B. A paper using the 1996–1998 data has been submitted to *International Journal of Epidemiology* and is included as Appendix 2.

Although the screening method has many potential sources of bias, trends in vaccine effectiveness may still be monitored over time, assuming these biases remain constant. Such ongoing monitoring will be important to evaluate vaccine effectiveness following Australia's change to an acellular vaccine. The method developed in this chapter for the vaccine effectiveness estimations could be incorporated into routine surveillance to monitor changes in vaccine effectiveness over time, and could also be applied to other vaccine-preventable diseases. This is the first Australian study of its kind and few international studies have used multivariate methods. Even where multivariate methods have been used, regional vaccine coverage data have not been available. The availability of regional coverage data, the accuracy of which has improved since 1996, means that this method is particularly useful in the Australian setting.

A summary of the main findings of the thesis and recommendations for further research are included in Chapter 7.

In an attempt to estimate the extent of under-notification of pertussis cases and to obtain an alternate incidence estimate for pertussis, I designed a cough survey in 5-14 year old children living in western Sydney. The study proposal for this survey is included as Appendix 1, *Study proposal for a survey of cough and pertussis immunisation status in children*. As data analysis is not complete and some of the results are included in another student's thesis, the results of this study are not presented here.

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Chapter 2

Pertussis in Australia: notifications, hospitalisations and deaths

Background

In this chapter I bring together the most recent routinely collected data on pertussis available nationally from three sources (notifications, hospitalisations and deaths), for all age groups in Australia. An earlier draft of this chapter was included in the *Communicable Diseases Intelligence* supplement *Vaccine preventable diseases and vaccination coverage in Australia, 1993-1998* .[1]

Methods

Notification data were obtained from the National Notifiable Diseases Surveillance System (NNDSS), hospitalisation data from the Australian Institute of Health and Welfare (AIHW) National Hospital Morbidity Database, and mortality data from the Australian Bureau of Statistics (ABS) Causes of Death Collection. SAS for Windows[2] and Excel[3] were used for the analyses.

Notifications

The NNDSS is coordinated by the National Centre for Disease Control, Commonwealth Department of Health and Aged Care. The NNDSS database was established in its current form in 1991, and includes cases of pertussis reported to State/Territory authorities under their current public health legislation. This legislation requires medical practitioners to notify cases of pertussis to the appropriate health authority. Laboratories in all States/Territories except Western Australia are also required by legislation to notify cases of pertussis. State/Territory notification criteria are based on the National Health and Medical Research Council (NHMRC) surveillance case definitions,[4] which for pertussis is:

- Isolation of *Bordetella pertussis* from a clinical specimen; or

- Elevated *Bordetella pertussis* specific IgA in serum or *Bordetella pertussis* antigen in a nasopharyngeal specimen using immunofluorescence with a history of clinically compatible illness; or

- An illness lasting 2 weeks or more with one of the following:
  - ⇒ Paroxysms of coughing,
  - ⇒ Inspiratory 'whoop' without other apparent causes,
  - ⇒ Post-tussive vomiting; or

- An illness characterised by a cough illness lasting at least 2 weeks in a patient who is epidemiologically related to a laboratory confirmed case.

Some States/Territories use variations of this case definition and the extent to which States and Territories verify that notified cases meet case definitions is unknown. This means there is no way of confirming that NNDSS notified cases uniformly meet the case definition criteria.

Unit record notification data for pertussis were extracted from NNDSS for cases with an onset between 1 January 1993 and 31 December 2000 (8 years). Data were updated in February 2001. Data for the year 2000 are preliminary and may therefore be subject to revision. The variables analysed were date of disease onset, age at onset, sex and State/Territory of residence. The fields for laboratory confirmation, date of birth, vaccination status and Aboriginality were too incomplete to warrant analysis.

Hospitalisations

Since July 1993, the AIHW National Hospital Morbidity Database has recorded administrative, demographic and clinical information on all patients admitted to public and private hospitals in Australia.[5] Cases discharged between 1 July 1993 and 30 June 1998 (5 years) were analysed. Cases admitted before 1 July 1993 were excluded, as were cases admitted in 1997/1998 but discharged after 30 June 1998. The variables extracted for analysis were date of admission (reported by financial year of admission, which in Australia starts at the beginning of July and ends at the end of June), age at admission (five year age group), sex, State/Territory of residence, State/Territory of hospitalisation, length of stay (LOS) and diagnosis (principal and other diagnoses — up to 26 diagnoses were recorded for each admission). Age in years was available for all States and Territories except South Australia and Queensland. As data on hospitalisations are collated by financial year of discharge from hospital, discharges for a particular year may include episodes of care for which the admission was in a previous year.[5] State/Territory of residence was not available for all records and so State/Territory of hospitalisation was used.

Data were extracted on the basis of International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM). The first Australian version of the ICD-

9-CM was used for the 1995/1996 data and the second version for 1996/1997 and 1997/1998 data. The ICD-9/ICD-9-CM code 033 (whooping cough) was used to identify pertussis hospitalisations. This code includes codes for *Bordetella pertussis* (033.0), *Bordetella parapertussis* (033.1) and whooping cough with no organism mentioned (033.9).

Deaths

Summary death data were obtained from the ABS Causes of Death Collection for those deaths coded with the ICD-9 code 033. The Causes of Death Collection classifies death records based on the reported underlying cause of death. Data were available for deaths registered from 1993 to the end of 1997 (5 years). The variables extracted for each death were age at death, year death was reported, sex and State/Territory in which death was recorded.

Calculations

Rates were calculated using ABS mid-year estimated resident populations. Rates are presented as annual rates or average annual rates per 100 000 total population or population in age, sex or geographic subgroups, as appropriate. Average annual rates were calculated by dividing the total number of cases for the period of investigation by the sum of each year's population for the same period. For hospitalisation data, the mid year population estimate for the first half of the financial year was used as the denominator. Averages were calculated for rates of notifications and hospitalisations, and for bed days per year. Medians and ranges, rather than averages, were used to describe the distribution of notifications and hospitalisations per month, and length of stay per admission, as these data were not normally distributed.

Results

Secular trends

There were 45 455 notifications of pertussis received by the NNDSS with dates of onset between 1 January 1993 and 31 December 2000. Pertussis notifications peaked in 1997 (*Figure 2.1*) when 10 907 cases were notified, approximately double the number in previous and following years. The median number of notifications was 416 cases per month, with a range from 115 to 1606. The average annual notification rate

for the eight year period was 30.9 per 100 000 population. The lowest rate was 23.2 in 1999 and the highest was 58.9 in 1997.

A seasonal pattern was apparent with the highest number of notifications occurring in the spring and summer months between August and February each year. Hospitalisations followed a similar pattern to notifications for the years in which hospitalisation data were available but there was less variation in the numbers of hospitalisations. Although a seasonal pattern was clearly apparent in school-aged children and in adults (5-14 & 15+ years), it was less obvious in pre-school aged children (0-4 years), particularly in the non-epidemic years (*Figure 2.2*).

Figure 2.1. Pertussis notifications, 1993–2000, and hospitalisations, July 1993–June 1998, by month of onset or admission, Australia
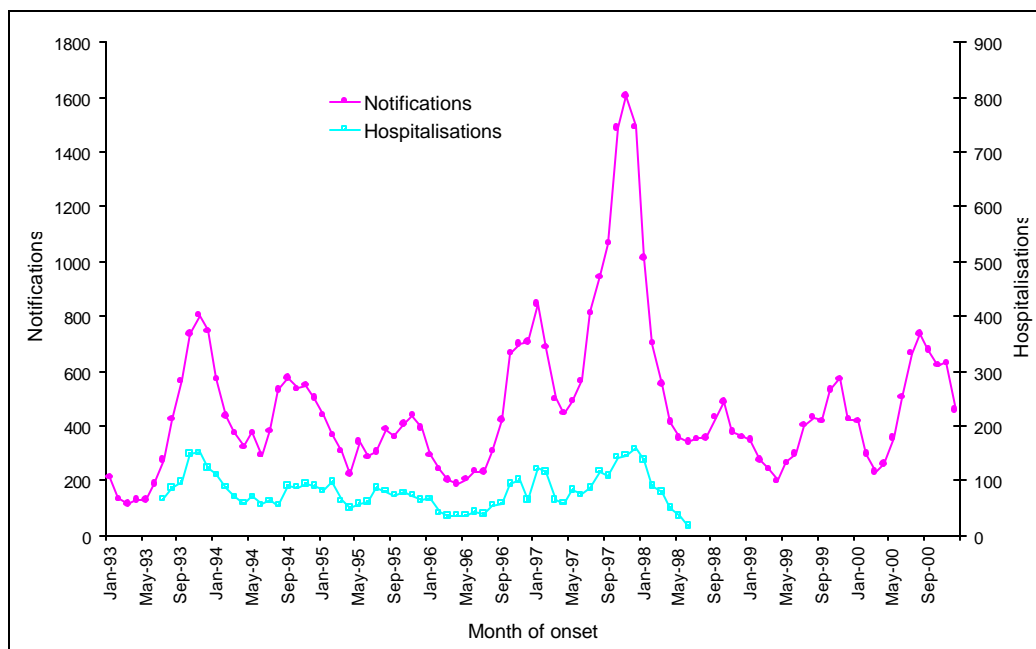
Note varying scales between notifications and hospitalisations.

Figure 2.2. Pertussis notifications by month of onset and age group, Australia, 1993–2000
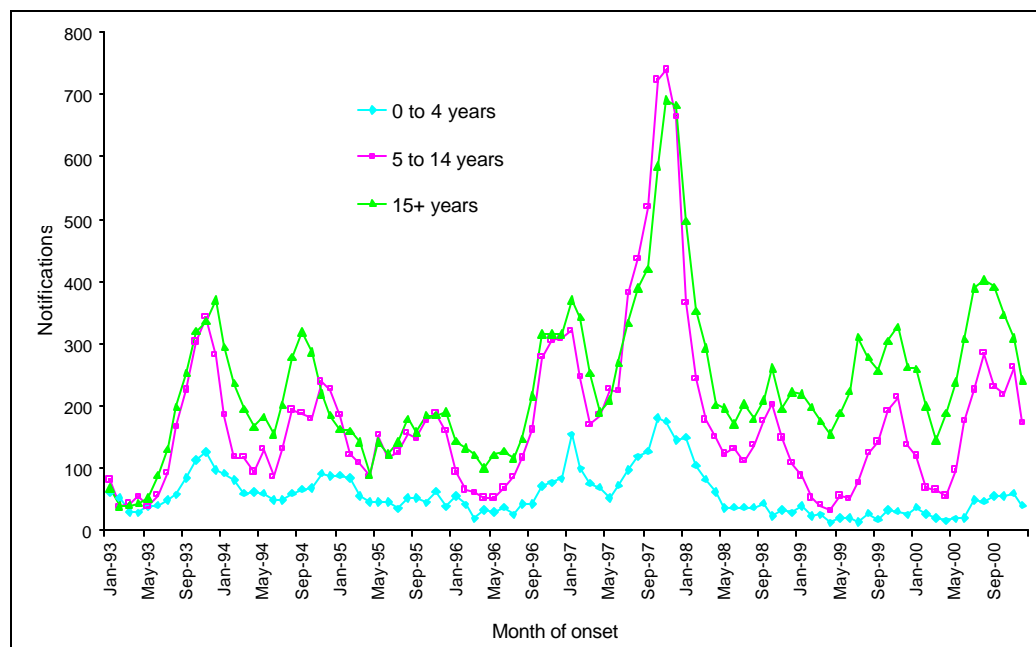
Severe morbidity and mortality

From July 1993 to June 1998, 4804 persons were hospitalised with pertussis (ICD-9/ICD-9-CM code 033, *Table 2.1*), compared with 31 709 pertussis notifications in the same period. Of the hospitalisations, 4014 (84%) had a principal diagnosis of pertussis (average annual rate 4.4 per 100 000 population). *Bordetella pertussis* (ICD-9/ICD-9-CM code 033.0) was recorded for 1429 (30%) hospitalisations and was the principal diagnosis for 1210 (25%). *Bordetella parapertussis* (033.1) was recorded for 55 (1%) hospitalisations and was the principal diagnosis in 25 (0.5%) cases. The remaining cases were coded as whooping cough (033.9). A total of 19 582 bed days (average 5263 days per year) were recorded for patients with pertussis. The median length of stay per admission was 3 days.

Table 2.1. Pertussis hospitalisations July 1993–June 1998 and deaths 1993–1997, by age group, Australia

Age group (years)	Hospitalisations July 1993–June 1998		LOS* per admission (days)	Deaths 1993–1997	
	Total (PD†)	Rate‡ (PD†)	Median	No.	Rate‡
0–4	3427 (3009)	52.9 (46.4)	3	9	0.1
5–14	741 (608)	5.7 (4.7)	2	0	-
15–24	108 (68)	0.8 (0.5)	3	0	-
25–59	345 (220)	0.8 (0.5)	4	0	-
60+	183 (109)	1.3 (0.8)	7	0	-
All ages	4804 (4014)	5.3 (4.4)	3	9	0.0

*LOS = length of stay in hospital.

† PD = principal diagnosis.

‡ Average annual age-specific rate per 100 000 population.

Between 1993 and 1997 there were nine deaths recorded as due to pertussis — one in 1995, two in 1996 and the remaining six in 1997. Five of the deaths were in New South Wales, two in Queensland and one each in Victoria and Western Australia.

Age and sex distribution

The highest notification rate for the period 1993–2000, was the 10–14 year old age group (*Figure 2.3*). However, infants aged less than one year had considerably higher notification rates than 1–4 year olds, and combining these two groups masks this important difference. When infants aged less than one year and 1–4 year olds are separated it is clear that the highest notification rate, both overall and for all years prior to 1999, was in infants aged less than one year (*Table 2.2 & Figure 2.4*). Infants aged less than one year accounted for 5% of all notifications and children aged less than five years for 12% (*Table 2.2*).

Figure 2.3. Pertussis notification rates by five year age group, Australia, 1993–2000
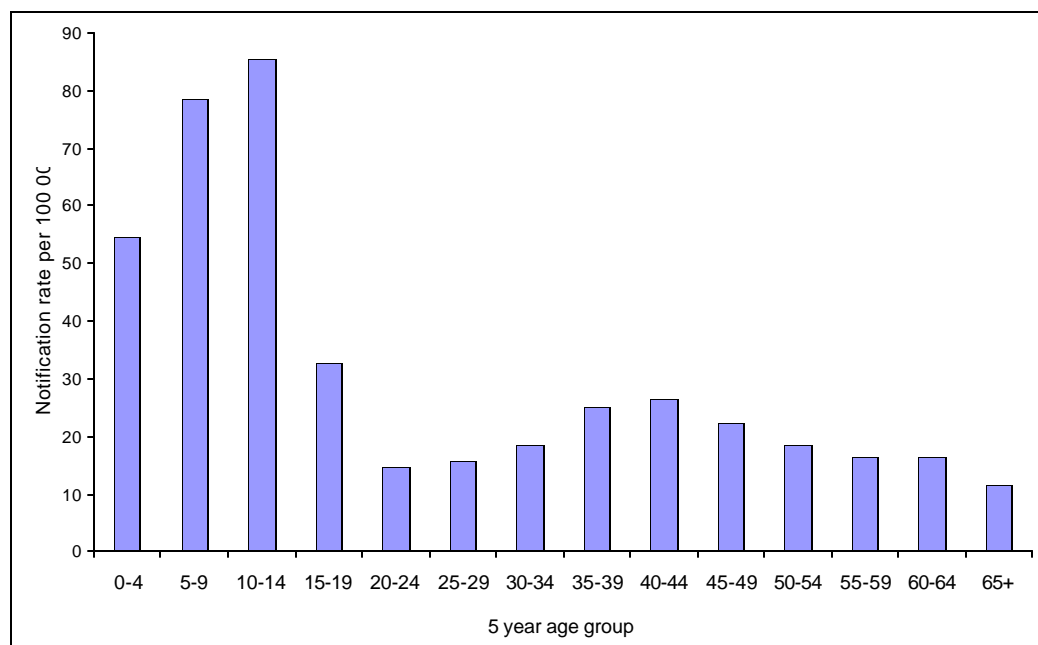
Table 2.2. Pertussis notifications and average annual notification rates, by age group, Australia, 1993–2000

Age group	Notifications		Average annual rate per
	n	%	100 000 population
<1 year	2 212	5	109
1-4 years	3 404	7	41
5-9 years	8 211	18	78
10–14 years	8 881	20	85
15+ years	22 747	50	20
Total	45 455	100	30

Figure 2.4. Pertussis age-specific notification rates by year of onset, Australia, 1993–2000
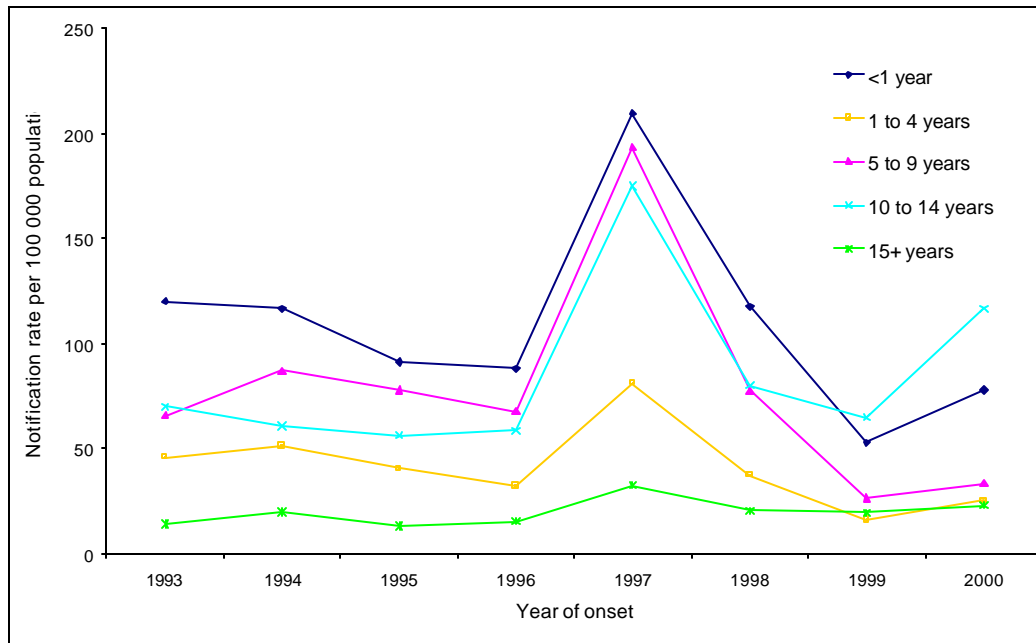
In contrast with notifications, a much greater proportion of hospitalisations were in young children, with children aged less than five years accounting for 71% of hospitalisations. Where year of age was available (all States and Territories except South Australia and Queensland), 61% of hospitalisations were in children aged less than one year (*Table 2.3*). The average annual hospitalisation rate for infants aged less than one year was 207 per 100 000 (*Table 2.4*). The number of infants aged less than one year hospitalised from July 1993 to June 1998 was 45% greater than the number notified in the same period (1965 hospitalisations compared with 1356 notifications). In infants aged less than one year hospitalisation rates were greater than notification rates for all years (*Figure 2.5*). All fatal cases of pertussis were in children aged less than 12 months.

Table 2.3. Pertussis hospitalisations b y State/Territory of residence and financial year of admission, Australia, July 1993–June 1998

Year	ACT	NSW	NT	Qld	SA	Tas	Vic	WA	Total
93/94	6	480	5	274	145	13	140	60	1123
94/95	12	238	45	253	52	21	157	107	885
95/96	5	199	11	171	86	15	164	57	708
96/97	7	261	3	88	157	8	275	124	923
97/98	9	439	8	213	123	11	125	237	1165
Total	39	1617	72	999	563	68	861	585	4804
<5 yr	28	1215	61	652	316	48	642	465	3427
<1 yr	24	963	50	N/A	N/A	41	525	362	1965

N/A=not available.

Table 2.4. Pertussis hospitalisation rate s per 100 000 population by State/Territory of residence and financial year of admission, Australia, July 1993–June 1998

Year	ACT	NSW	NT	Qld	SA	Tas	Vic	WA	Total
93/94	2.0	8.0	2.9	8.8	9.9	2.8	3.1	3.6	6.4
94/95	4.0	3.9	26.0	7.9	3.5	4.4	3.5	6.3	5.0
95/96	1.6	3.2	6.2	5.2	5.9	3.2	3.6	3.3	3.9
96/97	2.3	4.2	1.6	2.6	10.6	1.7	6.0	7.0	5.0
97/98	2.9	7.0	4.3	6.3	8.3	2.3	2.7	13.2	6.3
Total*	2.6	5.3	8.1	6.1	7.7	2.9	3.8	6.7	5.3
<5 yr*	25	55	69	55	64	28	40	73	53
<1 yr*	108	220	279	N/A	N/A	123	167	291	207

*Average annual rate.

Figure 2.5. Pertussis hospitalisation rates by age group (all ages) and notification rates in infants aged less than 1 year by financial year of admission/onset, Australia, July 1993–June 1998
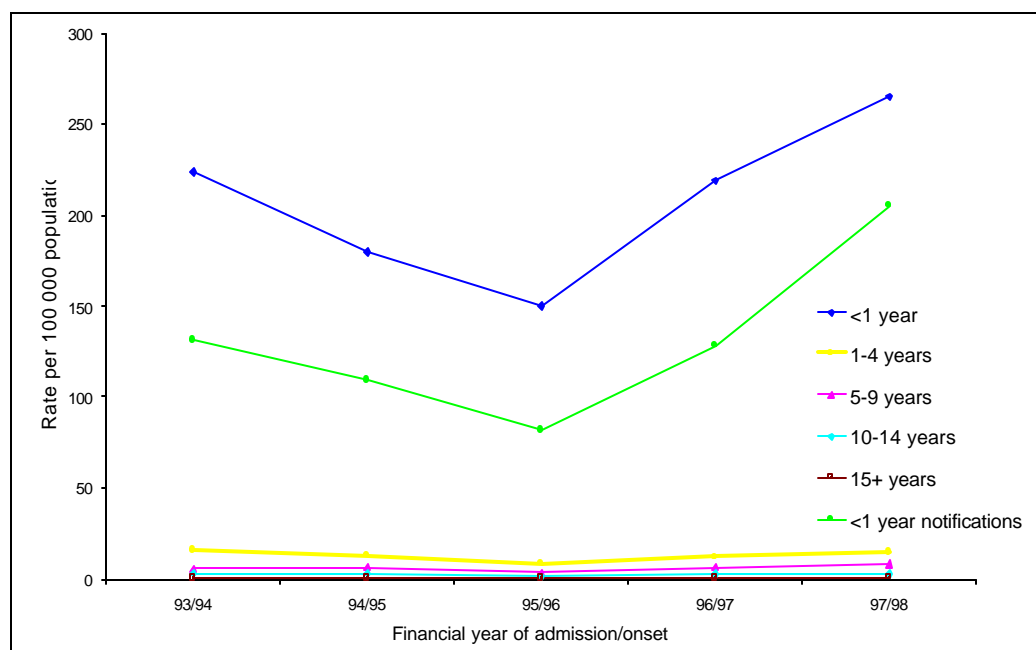
School-aged children (5–9 and 10–14 years) accounted for 38% of all notifications (compared with 15% of all hospital admissions, *Tables 2.1* & *2.2*) and had higher notification rates than any of the other five-year age groups (*Figure 2.3*). From 1996 to 1998, there was little difference between the notification rates among 5–9 year olds and 10–14 year olds (*Figure 2.4*). This contrasted with 1994 and 1995, when the rates for 5–9 year olds were approximately 40% higher than the rates for 10–14 year olds. However, in 1999 and 2000, the rate for 10–14 year olds was more than three times higher than for 5–9 year olds. In fact, in 1999 and 2000, 10–14 year olds had the highest notification rates of any age group, even exceeding those in infants aged less than 12 months. Within the 10–14 year age group, 11 year olds have had the highest notification rate since 1998.

Since the introduction of the fifth dose of pertussis vaccine for preschoolers in 1994, the distribution of notifications by year of age within the 5–9 year age group has shifted upwards. In 1993 and 1994, 5–6 year olds had higher notification rates than 7–9 and 10–14 year olds (*Figure 2.6*). In 1995, 5–6 and 7–9 year olds had equal rates which were higher than those for 10–14 year olds. However, since 1996 the rates

among 7–9 year olds have been higher than for 5–6 year olds. This difference was greatest in the years 1996 to 1998. Since 1999, the rates for 5–6 and 7–9 year olds have both been lower than for 10–14 year olds. This change in age distribution over time can be seen in more detail by examining notification rates by year of age in 5–11 year olds (*Figure 2.7*). In 2000, notification rates in this group increased with each increasing year of age. However, there was no meaningful difference in rates between 5–8 year olds, 9 year olds had only a slightly higher rate, but the 10 and 11 year olds had much higher rates.

Figure 2.6. Pertussis notification rates in 5–14 year olds by age group and year of onset, Australia, 1993–2000
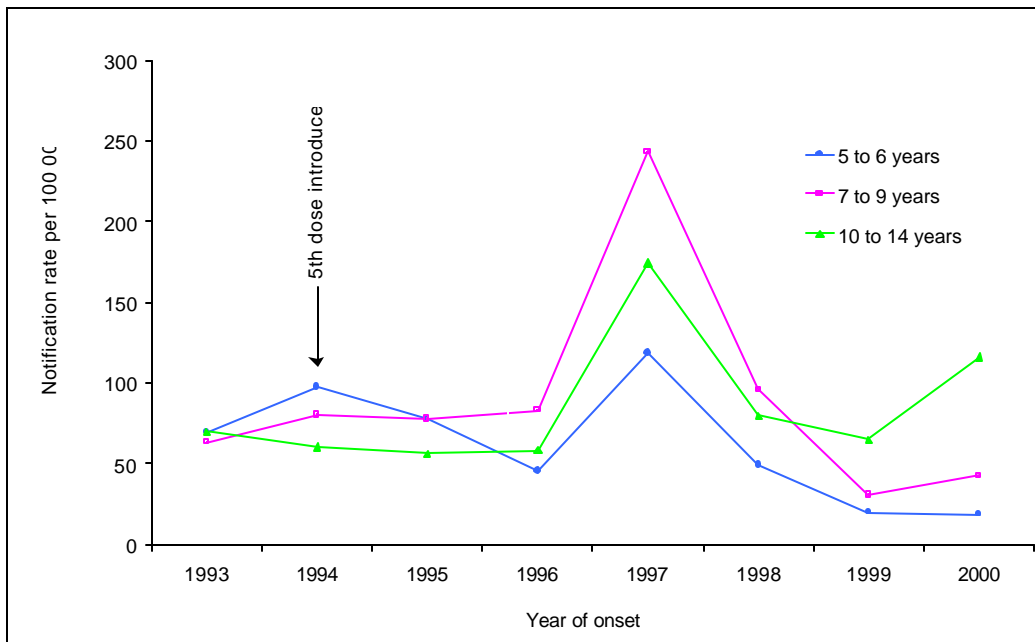
Figure 2.7. Pertussis notification rates in 5–11 year olds, by year of age and year of onset, Australia, 1993–2000
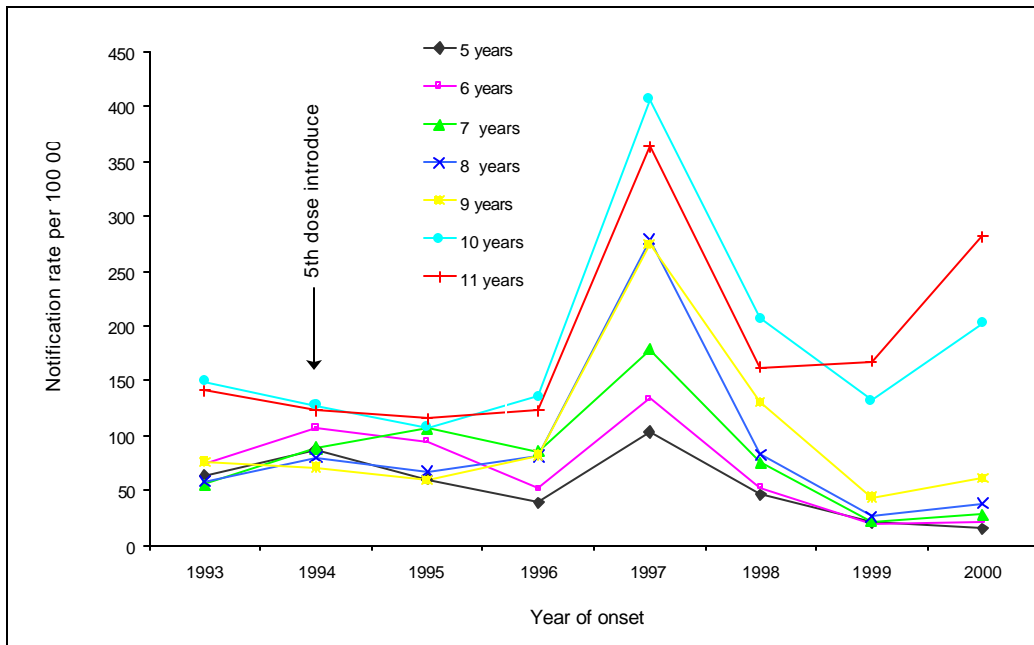
Adults (persons aged 15 years or more), like all age groups, experienced an increase in notification rates during the epidemic year of 1997. Although adults accounted for 50% of notifications, they had the lowest average annual notification rate (19.6 per 100 000, *Figure 2.4*). The adult notification rate was not consistent among all age groups (*Figure 2.3*). The 15–19 year olds had the highest adult notification rate (33 per 100 000), falling to 15 per 100 000 in 20–24 year olds. Rates then gradually increased, peaking at 26 per 100 000 in the 35–44 year old age group and then decreased down to 12 per 100 000 in persons aged 65 years and over.

Male to female ratio

The overall male to female ratio was 1:1.2 for notifications and 1:1.1 for hospitalisations. The number of female notifications exceeded the number of male notifications in all age groups, but the difference was greatest in the 25–45 year age groups, in which females accounted for over 60% of all notifications. However, of the nine deaths, all of which occurred in infants, seven were in males compared with only two in females.

Geographic variation

There was substantial variation in notification numbers and rates between regions and years (*Figures 2.8a & 2.8b, Tables 2.5 & 2.6*). South Australia had the highest overall notification rate. However the Northern Territory and Western Australia had the highest notification rates in children aged less than five years (*Table 2.6*).

Hospitalisation rates also varied considerably between jurisdictions (*Table 2.4*). As most pertussis hospitalisations were in children aged less than five years, the geographic distribution of hospitalisations and notifications for this age group was compared. Nationally, in children aged less than five years, the notification rate (58 per 100 000, *Table 2.6*) and hospitalisation rate (53 per 100 000, *Table 2.4*) were similar. However, hospitalisation rates exceeded notification rates in Queensland and Victoria. Western Australia had the highest average annual notification and hospitalisation rates, while Tasmania, the Australian Capital Territory and Victoria had the lowest rates (*Tables 2.4 & 2.6*). In infants aged less than one year, the number of hospitalisations were greater than the number of notifications for all jurisdictions where these data were available.

In New South Wales, South Australia, Victoria and Western Australia, the year with the highest number and rate of notifications was 1997 (*Tables 2.3 & 2.4, Figure 2.8*). In South Australia, Victoria and Western Australia, the financial years 1996/97 and 1997/98 also had the highest hospitalisation rates (*Table 2.4*). In the Northern Territory and Queensland, 1994 had the highest notification rates (*Table 2.6 & Figure 2.8*), with corresponding high hospitalisation rates (*Table 2.4*). The highest annual notification rate was 130 per 100 000, recorded in Tasmania in 1999 (*Table 2.6* — note that hospitalisation data for 1999 were not available for comparison). This was followed by 113 per 100 000 in South Australia in 1997 and 109 per 100 000 in the Northern Territory in 1994 (*Table 2.6*). The highest annual hospitalisation rate was 26 per 100 000, recorded in the Northern Territory in 1994/95 (*Table 2.4*). This was followed by 13.2 per 100 000 in Western Australia in 1997/98 and 10.6 per 100 000 in South Australia in 1996/97 (*Table 2.4*).

Figure 2.8a. Notification rates by State/Territory and year of onset, Australia, 1993–2000, Australian Capital Territory, New South Wales, Northern Territory and Western Australia
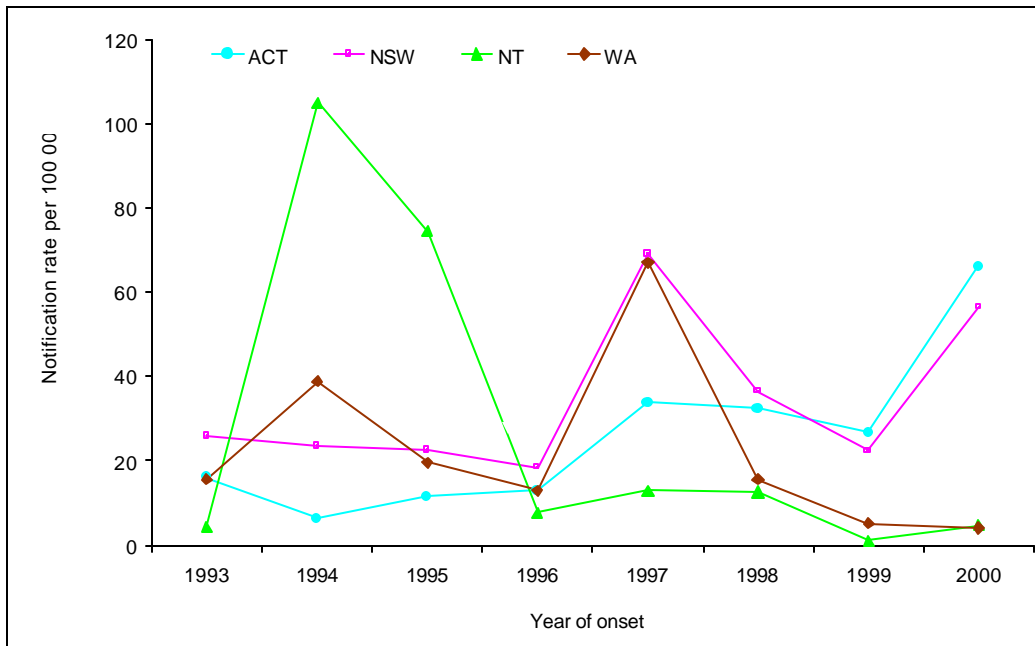
Figure 2.8b. Notification rates by State/Territory and year of onset, Australia, 1993–2000, Queensland, South Australia, Tasmania and Victoria
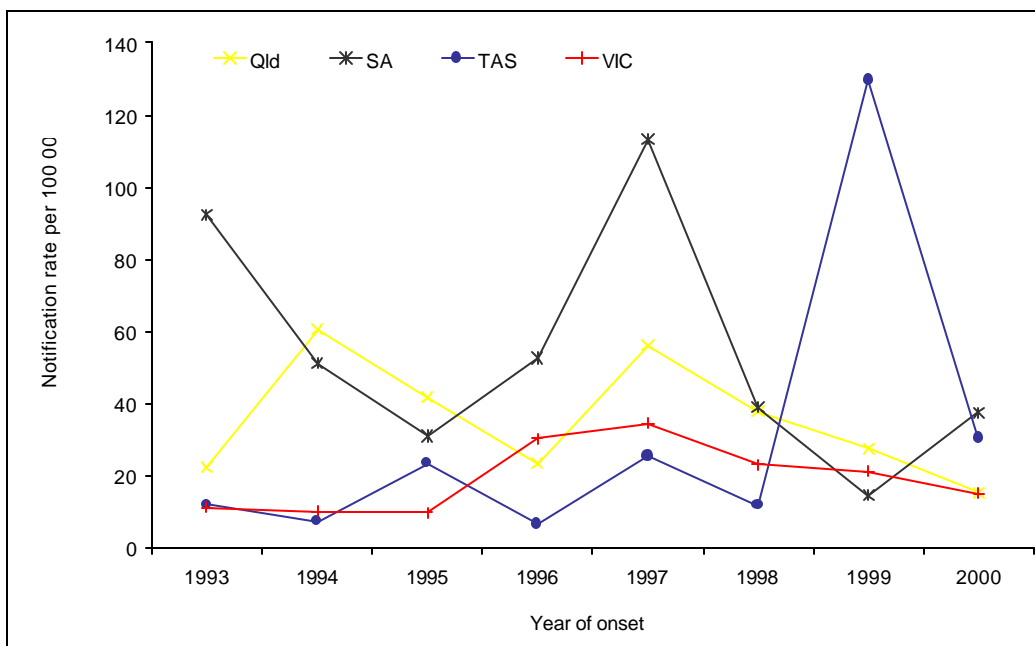
Table 2.5. Pertussis notifications by State/Territory and year of onset, Australia, 1993–2000

Year	ACT	NSW	NT	Qld	SA	Tas	Vic	WA	Total
1993	48	1 548	7	687	1 351	56	496	261	4 454
1994	19	1 427	182	1 923	748	34	448	662	5 443
1995	35	1 385	132	1 354	454	110	438	339	4 247
1996	40	1 146	14	774	774	31	1 378	227	4 384
1997	105	4 328	24	1 902	1 675	120	1 584	1 204	10 942
1998	100	2 313	24	1 306	579	55	1 078	284	5 739
1999	83	1 429	2	963	217	610	998	96	4 398
2000	205	3 616	9	532	558	143	710	75	5 848
Total	635	17 192	394	9 441	6 356	1 159	7 130	3 148	45 455
<5yr	52	1 678	86	696	440	73	728	729	4 482
<1yr	25	881	46	208	201	35	506	310	2 212

Table 2.6. Pertussis notification rates per 100 000 population by State/Territory and year of onset, Australia, 1993–2000

Year	ACT	NSW	NT	Qld	SA	Tas	Vic	WA	Total
1993	16.0	25.8	4.1	22.1	92.5	11.9	11.1	15.6	25.2
1994	6.3	23.5	105.0	60.3	51.0	7.2	10.0	38.9	30.5
1995	11.5	22.6	74.3	41.5	30.9	23.2	9.7	19.6	23.5
1996	13.0	18.5	7.7	23.2	52.5	6.5	30.2	12.9	23.9
1997	33.9	69.0	12.8	55.9	113.2	25.3	34.4	67.0	59.1
1998	32.4	36.5	12.6	37.8	38.9	11.7	23.1	15.5	30.6
1999	26.8	22.3	1.0	27.4	14.5	129.7	21.2	5.2	23.2
2000	66.1	56.4	4.7	15.1	37.4	30.4	15.1	4.0	30.8
Total*	25.9	34.5	26.9	35.2	53.8	30.7	19.4	22.1	30.9
<5yr*	39.1	63.7	81.3	48.4	75.1	35.7	38.2	95.9	57.7
<1yr*	70.9	127.6	160.5	55.3	132.4	67.9	102.9	155.6	109.2

*Average annual rate.

Discussion

The greatest burden of pertussis is borne by infants aged less than one year, amongst whom the average annual notification rate was 109 per 100 000, with rates remaining high throughout the study period. This group had an even higher hospitalisation rate (207 per 100 000) and accounted for the majority of hospitalisations (61%) and all the deaths. This is clearly the group requiring the greatest protection from pertussis infection.

Notification rates are known to underestimate incidence. This is illustrated by the finding that the number of hospitalisations in infants aged less than one year exceeded the number of notifications. In spite of this age group having the greatest need of protection from pertussis and therefore requiring careful monitoring, these data clearly show substantial under-notification. Hospitalisation data may be more useful than notification data as an indicator of pertussis incidence in this age group. The notification and hospitalisation patterns in young children were similar to those during

an epidemic in New Zealand where, from June 1995 to May 1997, children aged less than 15 months accounted for 82% of hospitalisations but only 21% of notifications.[6]

Temporal and geographic distribution

The highest numbers of pertussis notifications were seen in 1997, with most jurisdictions experiencing an epidemic in that year. This epidemic affected all age groups with more deaths recorded than in any other year since 1960.[7] The State and Territory which did not experience an epidemic in 1997 were the Northern Territory, where 1994 was an epidemic year, and Tasmania, where an epidemic occurred in 1999. Tasmania and the Northern Territory both have small populations and low population densities and are relatively isolated, so it is not surprising that these areas experienced outbreaks in different years to other States and Territories. Jurisdictions with these characteristics may also experience outbreaks less often. Even within a State/Territory, isolated communities may exist which may not follow the pattern of the State/Territory. Such was the case in a community in the north-west of Western Australia, which experienced a pertussis outbreak in late 1999.[8] Prior to this outbreak, there had been no notified cases of pertussis in this community since 1988, despite an epidemic in the rest of the State in 1997.[8]

Where the data were available, areas and years with high notification rates also tended to have high hospitalisation rates, especially among infants, suggesting that notifications reflect incidence. As pertussis epidemics tend to occur in three to four year cycles, some variation by geographic area is to be expected depending upon the timing of the last epidemic and also on geographic differences in past or present pertussis vaccination coverage.

Some of the observed differences in notification rates between jurisdictions may also reflect differences in surveillance methodologies. Some jurisdictions may be more active than others in case-finding, particularly during an outbreak. The use of serological tests for diagnosis may vary between jurisdictions. This would have the greatest impact on adolescent and adult notification rates and the least impact on infants aged less than 12 months (see Chapter 3 for a discussion of diagnostic tests). Information on method of diagnosis is useful when making comparisons and interpreting trends over time. Unfortunately, information on the method of diagnosis

is not currently collected at a national level. However, the NNDSS is being upgraded so that this information can be collected nationally in the future.

Adult pertussis

Adults (≥15 years of age) accounted for half the notifications and 13% of the hospitalisations. Pertussis in adolescents and adults has been documented for many years in many countries, so is not a new phenomenon.[9-15] The proportion of adolescent and adult pertussis cases in Australia during this review period was far greater than that in the United States.[16] This is probably due to older persons in the United States being less likely to be notified than in Australia, as the United States does not include serological diagnosis in its case definition. The proportion of adolescent and adult cases in Australia is also greater than in the Netherlands.[17] In the Netherlands, serological diagnosis is included, but the serological case definition is much stricter than in Australia and requires a significant increase (at least fourfold) in antibody levels.[18]

Since the early 1990s, a commercially available enzyme-linked immunosorbent assay (ELISA) for IgA against whole-cell *B. pertussis* has been widely used in diagnostic laboratories throughout Australia. Australia is unique in having serological tests for pertussis widely available through public and private sector laboratories. Although the validity of these tests is difficult to evaluate without a diagnostic reference standard, a study undertaken in western Sydney found that cases notified on the basis of positive whole-cell serology reported clinically consistent pertussis almost uniformly.[19] The results of the western Sydney study suggest that notifications based on positive serology underestimate, rather than overestimate, the true incidence of pertussis.[19] Up until 1997, no ELISA technique for the routine diagnosis of pertussis was approved in the United States.[20]

No significant rise in adult notifications was seen in the review period. However, adult notifications increased in South Australia just prior to 1993, corresponding with an increased use of serological tests.[21] Surveillance data from various other countries indicate that an increasing proportion of reported cases are occurring in adolescents and adults.[22] In the United States, the incidence of notified adolescent and adult pertussis cases has recently increased, with the incidence among persons aged ten

years and older doubling during 1994–1996 compared with 1990–1993.[11] The contrast in the proportion of adolescent and adult cases between Massachusetts and the rest of the United States was striking, with Massachusetts accounting for 23% of cases in persons aged 10 years and older from 1989 to 1998, in spite of Massachusetts constituting only 2% of the national population.[23] The incidence of notified cases in Massachusetts in 1998 was 70.9 per 100 000 in adolescents (10–19 years of age) and 5.0 in adults (≥20 years), much greater than national rates of 5.0 for adolescents (11–19 years of age) and 0.82 in adults (≥20 years).[23] Interestingly, and in contrast with the rest of the United States, since late 1997 the Massachusetts State Laboratory Institute of the Massachusetts Department of Public Health has performed a single-serum ELISA for IgG to pertussis toxin in person 11 years of age and over.[11,23] These differences highlight the importance of diagnostic criteria when making comparisons. The adolescent rates in Massachusetts in 1998 were higher than Australia's rates from 1993–2000 (59.0 per 100 000 in 10–19 year olds) but the adult rates in Massachusetts were lower than those in Australia (18.3 per 100 000).

Although the morbidity of pertussis is well known in children, far less is known about the morbidity in adolescents and adults.[24,25] A Canadian study of 664 adolescents and adults notified as having pertussis found that the mean duration of cough was 10 weeks in adolescents and 12 weeks in adults, 97% of cases coughed for three weeks or longer and 52% coughed for nine weeks or longer.[24] Other symptoms included post-tussive apnoea (87%), inspiratory whoop (69%), post-tussive vomiting (65%), rhinorrhoea (49%), pharyngitis (46%), sweating attack (32%), fever (31%) and fatigue (21%).[24] Complications from this group of adolescents and adults included sinusitis (13%), otitis media (4%), urinary incontinence (4%), pneumonia (4%), weight loss (3%), rib fracture (2%) and fainting (2%).[24] Authors of a study of notified cases in western Sydney described similar findings.[25]

In addition to the unpleasant symptoms and complications of pertussis in adults, there may be considerable work and social disruption. In the western Sydney study, 71% (34/48) of employed adults lost work days because of the illness, with a mean of ten work days lost for each employed adult.[25] Notified cases generally represent the more severe end of the clinical spectrum, even more so in adolescents and adults than in

younger children as many of the classical symptoms may not be present. In the Canadian study, a surprisingly high proportion (30%) of the passively reported adolescent and adult cases were culture-positive.[24] Because adults may not suffer from the classic pertussis symptoms and there may be a perception that pertussis is a childhood disease, a diagnosis of pertussis is frequently not considered.[13] In a study undertaken amongst university students in the United States, 26% of students with a cough lasting one week or longer had serological evidence of pertussis infection.[9] Similarly, in a study undertaken in New South Wales in 1985/1986, 26% of adults with a cough lasting one month or longer, who had been referred to a consultant physician, had serological evidence of pertussis infection.[10] Another study undertaken in the United States, this time of patients presenting to a hospital emergency department with a cough lasting two weeks or longer, found that 21% (16 of 75 patients) met the serologic criteria for pertussis infection, reinforcing the notion that pertussis is a common cause of persistent cough in adults and should be considered in the differential diagnosis.[13]

One of the main concerns of such high levels of adult pertussis is that adults may serve as a reservoir for pertussis in susceptible children. The overall secondary attack rate in household contacts in the Canadian study was 15% but was higher in children (29% in 0-4 year olds and 25% in 5–11 year olds) and particularly high in infants aged less than 12 months (43%).[24] The secondary attack rate in adult household contacts in a German study, which was based around a vaccine trial rather than passively notified cases, was 26.7%.[12] Therefore reducing adult pertussis would prevent morbidity not only among adults, but also among children, particularly infants who are at most risk of serious disease.

Impact of the fifth dose

Prior to the introduction of the fifth dose of diphtheria-tetanus-pertussis (DTP) vaccine in late 1994 (this is a preschool dose so few children would have received it before the beginning of 1995), the 1–4 year age group was the most completely vaccinated group and, amongst persons aged less than 15 years, had the lowest notification rates. This is evidence of an effect of vaccination. After the introduction of the fifth dose, as more of the 5–9 year age group became immune, the gap between

the 1–4 and 5–9 year age groups narrowed, and by 1999 the notification rates of the two age groups were similar.

The notification rate for 5–6 year olds was higher than for 7–9 year olds before the introduction of the fifth dose. By 1996, when most of the 5–6 year olds would have been eligible for a fifth dose, the rates were equal. Then, as relatively more of the 5-6 year olds would have received a fifth dose compared with 7–9 year olds, the rates for 5–6 year olds dropped considerably lower than 7–9 year olds. As more of the 7–9 year olds became eligible to have received the fifth dose, the gap narrowed such that by 1999 the 7–9 year olds had only a slightly higher rate than 5–6 year olds. In the year 2000, by which time all the 5–9 year olds would have been eligible to have received the fifth dose, the notification rates in this group increased with each increasing year of age. This increase in notifications with time since eligibility for vaccination could be suggestive of waning immunity, improved coverage with the fifth dose each year following its introduction or a combination of the two. The trend suggesting an impact of the fifth dose was first reported in 1997.[26] The relative rates within the 5–9 year olds, together with the overall reduction in notification rates for 5–9 year old, relative to rates in 10–14 year olds, provides further evidence of an impact from the introduction of the fifth dose of pertussis vaccine for pre-schoolers.

It will be important to monitor notification rates in the 10–14 year age group carefully as the cohort of children eligible for the fifth dose enter this age group. Children who were five years of age in 1995, and hence would have been eligible for the fifth dose, would have been ten years of age in the year 2000. In spite of this, rates among ten year olds increased rather than decreased in 2000, although they still remained less than rates among eleven year olds. Also, uptake of the fifth dose was low when this cohort (children aged ten years in 2000) was aged five years (see Chapter 4). Information on the vaccination status of these cases would clearly aid the interpretation of these trends. If the vaccine provides only short-term immunity (say 5 years) then a decrease in the 10–14 year old notification rates may not be observed. If there is no change in these rates, an additional pertussis booster in adolescence, as has been implemented in France,[27] may need to be considered.

Adult and adolescent booster

A combined diphtheria-tetanus-acellular pertussis vaccine (dTpa — the lower case letters indicating a reduced dose compared with child formulations), Boostrix™ manufactured by GlaxoSmithKline, was recently licensed (March 2001) for use for booster vaccination of persons aged ten years and over in Australia. At present there are no national recommendations for the use of this vaccine. Currently, a booster dose of diphtheria and tetanus is recommended for 15–19 year olds.[28] Immunity from the diphtheria-tetanus booster is long lasting, provided all previous doses have been given, and another booster is not required until 50 years of age.[28] Now that Boostrix™ is available, consideration is being given to replacing this diphtheria-tetanus booster with Boostrix.™

In contrast to the diphtheria and tetanus components of the vaccine, immunity from pertussis is not long lasting. The relatively short period of immunity to pertussis poses problems for maintaining adequate protection from pertussis in adults. If the pertussis vaccine provides shorter term immunity than infection with the disease, then routine boosting of adolescents with Boostrix™ may merely shift the age distribution of pertussis. This would mean that instead of 10–14 year olds having the highest notification rate for pertussis it could be persons in their twenties. This older age group are more likely than 10–14 year olds to become parents, hence infants, who require the greatest protection from pertussis exposure, could in fact have greater exposure to the disease. However, there may be a role for a pertussis booster for prospective or new parents and select occupational groups such as health-care workers, school teachers and childcare workers.

Male to female ratio

The reason for female notifications exceeding male notifications in all age groups is not clear. Where this difference was the most noticeable, in the 25–45 year age group, it may be at least partly explained by more females in this age group having closer contact with children than males, as females are more commonly the primary care giver. In addition, professions with substantial contact with children, such as teachers or childcare workers, generally have a greater proportion of females than males. Hence females may be more exposed to pertussis.

Limitations of the data

Comparisons between the notification, hospitalisation and death data should be made with caution as these databases differ in their purpose, reporting mechanisms and accuracy. To provide the most recent information available and to account for the varied reporting formats, different time periods have been reviewed for each data set. As there were no unique identifying codes to link records for the same individual across data bases and because of differences in the accuracy of each data base, it was not possible to analyse deaths and hospitalisations as a subset of notifications.

The rates presented here are crude rates and may be confounded by jurisdictional differences in the population structure, such as age, ethnicity and population density. It is also important to note that jurisdictions with small populations may have high rates even with low absolute numbers of cases, so that a small change in numbers results in a large change in rates. As the data presented here are not random samples that are subject to sampling variability, confidence intervals were not calculated.

A major limitation of the notification data is that they represent only a proportion of the total cases occurring in the community. Data accuracy may also vary between States/Territories due to the use of different surveillance methods. In addition, data accuracy may change over time as new diagnostic tests are introduced or surveillance practices change. Information on the method of diagnosis is not collected. This information would aid the interpretation of the data. In interpreting the geographic distribution of notification data, it is important to note that Western Australia, while receiving some laboratory notifications, is the only State/Territory that does not have legislation for mandatory laboratory notification.

Comparisons over time and between jurisdictions should be more valid for hospitalisation data than for notification data, because methods of collecting hospitalisation data are more uniform. However, some variation in hospital access, admission practices and record coding may occur between regions and over time. There are also limitations associated with the use of ICD-9 codes to identify cases. Hospital coding errors have been reported to occur at a frequency of at least 40%, and to be more common for diseases with which the coder is less familiar (eg, rare

diseases) and for admissions with multiple diagnoses.[29] Assignation of codes is based on information in medical records, as recorded by clinicians, and there are no strict case definitions. This is in contrast to the more stringent case definitions used for notification data, although it is not possible to determine whether these case definitions have been applied. It must also be noted that the hospitalisation data base contains a record for each admission, which means that there are separate records for each re-admission or inter-hospital transfer. Unique identifiers were not available and so some re-admissions may have been included. This is unlikely to have a major impact on case numbers for pertussis, as it is an acute illness. For hospitalisations where the pertussis code was not the principal diagnosis, the pertussis code will have been recorded as a co-morbidity (additional or secondary diagnosis), the relative importance of which cannot be gauged.

Age in months was not available for either the hospitalisation or notification data. From the New South Wales hospitalisation data collected at a State level (see Chapter 3) it can be seen that hospitalisations in 0–5 month olds were nearly six times higher than in 6–11 month olds. Since 1996, attempts have been made to collect date of birth in NNDSS. At present these data are too incomplete to warrant analysis but as data collection improves these analyses will be possible. Vaccination status is clearly essential information and attempts to collect this in a uniform manner are currently under way.

The problems associated with using ICD-9 codes to select hospitalisations may also apply to the causes of death data held by the Australian Bureau of Statistics. However, unlike hospitalisations, only a single underlying cause of death was recorded until 1997. Hence some deaths for which an ICD-9 code for pertussis was recorded may be missed if this code was not recorded as the underlying cause of death.

Conclusions

Routinely collected data, although they have limitations, provide comprehensive information about pertussis. Although pertussis notifications underestimate incidence considerably, the similarities in geographic and temporal trends in notifications and hospitalisations, especially amongst infants aged less than one year, suggest that these trends are real. The adoption of uniform case definitions and methods of

ascertainment throughout Australia, or at least the provision of information on the method of diagnosis, would improve our ability to accurately interpret national notification data. In the future, when date of birth and vaccination status of notified cases are adequately recorded, more in-depth analyses will be possible.

Pertussis remains a cause of considerable morbidity, especially in infants aged less than one year. Over the time period studied there have been some changes in the age-specific notification rates. The reduction in notifications among 5–9 year olds suggests an effect of the introduction of the fifth dose for pre-schoolers in 1994. Rates in adolescents are now the highest of any age group and need to be monitored closely. Although adult pertussis rates are relatively low, they account for half the number of notifications. As adults with pertussis may serve as reservoirs of infection, continuing the circulation of the organism in the community, reducing the incidence in this age group may be an important goal of future vaccination strategies.

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Chapter 3

Pertussis notifications and hospitalisations in New South Wales

Background

In this chapter I present the analyses of pertussis notification and hospitalisation data from New South Wales (NSW) between 1993 and 1999. Although NSW notifications and hospitalisations were included as part of the national data (Chapter 2), they warranted additional analyses, as more information about cases was recorded at a State level compared with the national data. Additional fields included in the NSW Notifiable Diseases Database (NDD) included age in months, method of diagnosis, the number of doses of pertussis-containing vaccine received, whether the case was hospitalised and health area of residence. The NSW hospitalisation database included age in months and health area of residence, neither of which was available from the national hospitalisation data. This additional information allowed analyses to be undertaken at the State level which were not possible at the national level.

NSW is divided into 17 health areas, eight of which are classified as rural (*Figure 6.1*). Each health area has a public health unit whose responsibilities include pertussis notifications for their area. Each public health unit enters information onto the NDD. Public health units may vary in size and function, depending upon the health needs and priorities of the area.

Infants generally suffer the greatest morbidity from pertussis, so it is helpful to know the age in months of infant cases. Also, because the primary vaccination schedule is given during the first six months of life, the pattern of disease among infants can give an indication of the effectiveness of vaccination programs. In order to determine whether cases are due to vaccine failure or failure to vaccinate, it is important to know whether childhood cases of pertussis are vaccinated and, if so, how many doses of the vaccine they have received. Use of the vaccination status data is further developed in the vaccine effectiveness chapter.

In order to interpret trends in pertussis notifications over time and to make comparisons with other countries, it is helpful to know the method of diagnosis of notified cases. A paper describing South Australian notification, hospitalisation and mortality data concluded that the increase in notifications from 1993–1996

represented increased serological testing rather than an increase in pertussis incidence.[1]

This chapter uses the additional data fields to provide a more in-depth analysis of NSW notification data than was possible with the national notification data. It also aims to examine age-specific notification and hospitalisation rates, particularly in cases aged 0 to 23 months, to look for variation in rates between health areas and, using notification data, to examine differences in methods of diagnosis over time and between age groups.

Methods

Notifications

All notified cases of pertussis with disease onset dates between 1 January 1993 and 31 December 1999 were selected from the NDD in the Health Outcomes and Information Statistical Toolkit (HOIST), NSW Department of Health. These data were downloaded from HOIST in March 2000. SAS for Windows[2] and Excel[3] were used for the analyses.

There are two fields pertaining to method of diagnosis in NDD. The first field, 'LABCONF', relates to whether a case is laboratory confirmed (yes/no category) whilst a second field, 'IDENMTHD', contains information on the method of identification. The method of identification field has nine categories, only one of which may be selected. These categories are: serology, antigen detected, clinical, culture, histopathology, microscopy, radiologically active, unknown and, since 1999, polymerase chain reaction (PCR). For most analyses, the categories radiologically active, histopathology, antigen detected and microscopy were re-categorised as 'other'. Cases whose method of diagnosis was 'unknown' or missing *and* were recorded as not laboratory confirmed were assumed to have been identified on clinical grounds and re-categorised as such.

Month of age was calculated by multiplying the NDD variable 'AGE', which gives year of age to 10 decimal places, by 12 and then specifying that the month of age variable is an integer to prevent rounding.

Hospitalisations

Data on pertussis cases discharged from hospital from between July 1993 and June 2000 were obtained from the NSW Department of Health Inpatient Statistics Collection Online System (ISCOS) by financial year of discharge and age in months on admission. For infants aged less than 12 months, data were also obtained by health area of residence. From 1993 to June 1998, the ICD-9/ICD-9-CM code 033 (whooping cough) was used to identify hospitalisations and deaths (the same as for the national data). From July 1998 to June 2000 the ICD-10-AM code A37 was used. This code includes codes for *Bordetella pertussis* (A37.0), *Bordetella parapertussis* (A37.1) and whooping cough with no organism mentioned (A37.9).

Calculations

Rates were calculated using Australian Bureau of Statistics (ABS) mid-year estimated resident populations for NSW, downloaded from HOIST, for the years 1993–1999 by five-year age group and health area. Where population data were required in smaller age groups than those provided by the ABS, the broader age group was divided proportionally to the required age group. For example, to calculate the population by month of age, the population figure for the 0–4 year age group (0–59 months) was divided by 60. Rates are presented as annual rates or average annual rates per 100 000 total population or population in age or geographic subgroups, as appropriate. Average annual rates were calculated by dividing the total number of cases for the period of investigation by the sum of each year's population for the same period. For hospitalisation data, the mid year population estimate for the first half of the financial year was used as the denominator.

Results

Notifications

Between January 1993 and December 1999, 13 456 cases of pertussis were notified to the NSW Health Department. Notifications peaked in the spring and summer months of 1993/1994 and again, with an even greater number of notifications, in 1997/1998 (*Figure 3.1*). The average annual rate for the entire period was 31 notifications per 100 000 population. Of the 13 456 cases, 563 (4%) were recorded as being admitted

to a hospital and 320 of the hospitalised cases (57%) were infants aged less than one year. Only one case was recorded as having died as a result of pertussis infection.

Figure 3.1. Pertussis notifications by month of onset, NSW, 1993–1999
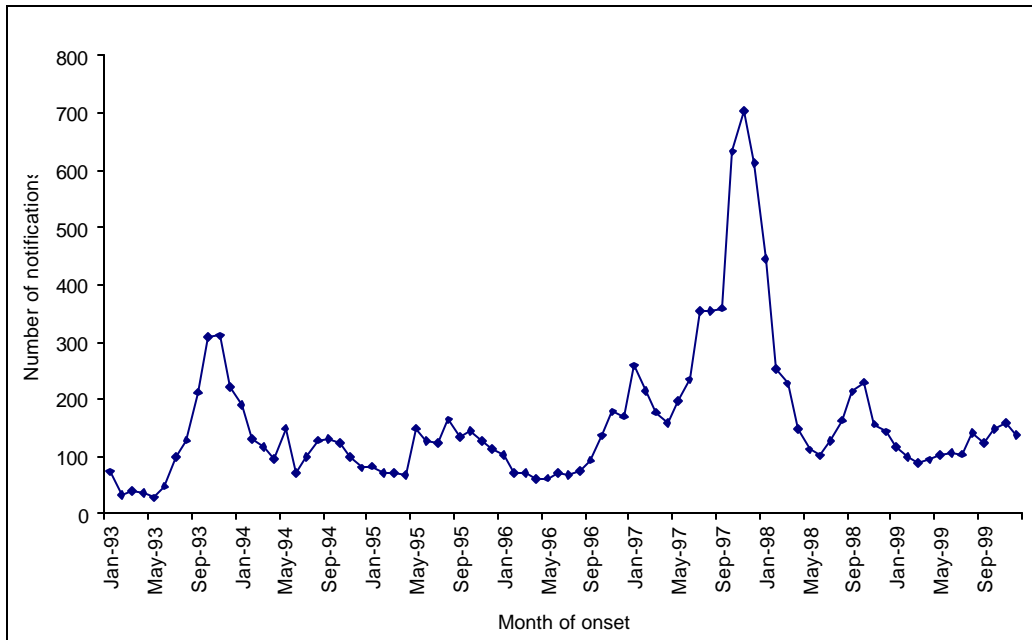
Age distribution

Infants aged less than one year had the highest notification rate, followed by school aged children (*Table 3.1*). All age groups experienced an increase in notification rates during the epidemic year of 1997 (*Figure 3.2*). The adult (aged ≥15 years) notification rate was higher in 1997–1999 than in 1993–1996. Following the introduction of the fifth dose of DTP for 4-5 year olds in 1995, the notification rate in 5 and 6 year olds fell below that for the 7–9 year olds, falling to the same rate as the 10–14 year olds in 1996. Since 1996, the notification rate in 4–5 year olds has remained below that for 7–14 year olds (*Figure 3.3*). In 1999, the notification rate in 7–9 year olds fell below the rates for 10–14 year olds who, in 1999, had a notification rate only just below that for infants aged less than 12 months.

Table 3.1. Pertussis notifications and average annual notification rates, by age group, NSW, 1993–1999

Age group	Notifications		Average annual rate
	n	%	per 100 000
<1 year	773	6	126
1-4 years	1 105	8	45
5-9 years	2 718	20	89
10–14 years	2 225	17	74
15+ years	6 632	49	19
Total	13 453	100	31

Figure 3.2. Pertussis notification rates by age group and year of onset, NSW, 1993– 1999
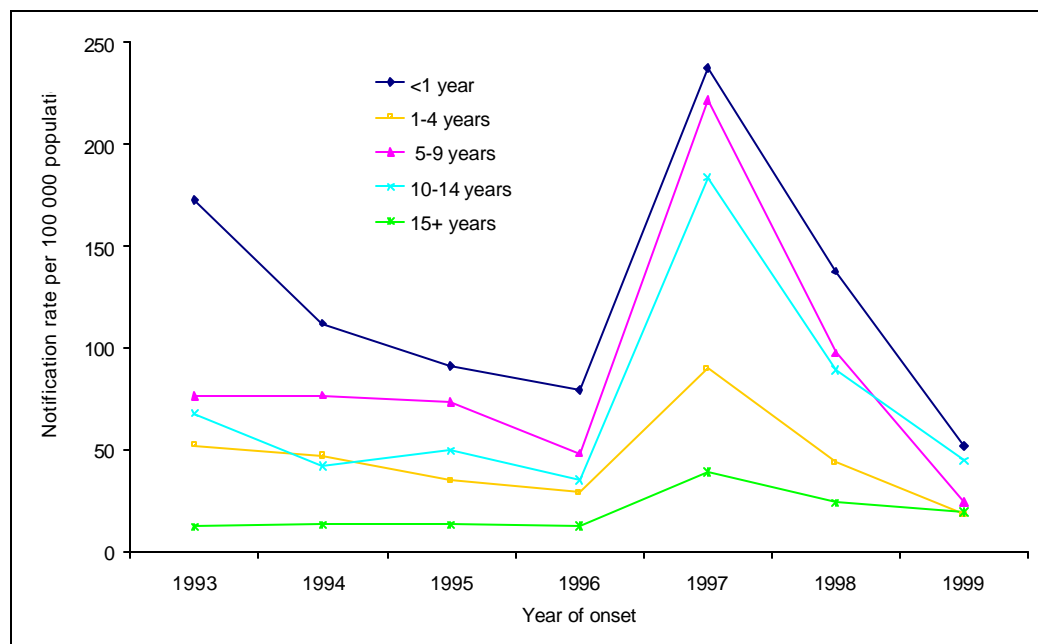
Figure 3.3. Pertussis notification rates for 5 – 14 year olds by age group and year of onset, NSW, 1993 – 1999
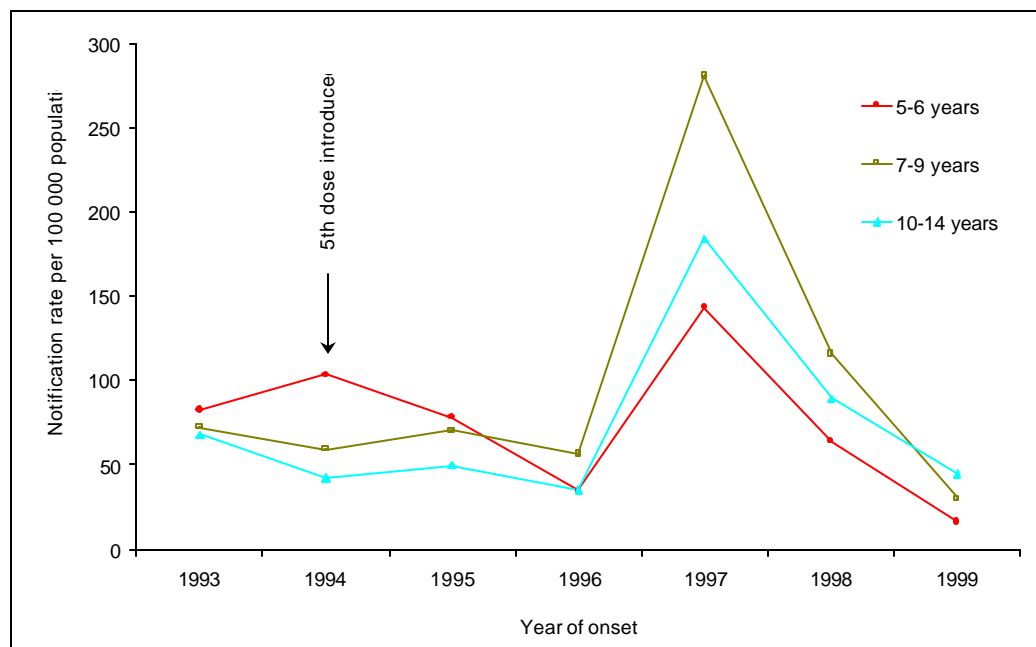
Children aged under 2 years

During the period 1993–1999, in children aged less than two years, there was an overall downward trend in average annual notification rates by month of age, although the rates did not always decrease with increasing age (*Figure 3.4*). When the average annual notification rate in five age groups corresponding with eligibility to receive 0, 1, 2, 3 and 4 doses of the vaccine was examined the downward trend was clear, with infants aged less than 2 months having the highest rates and those aged 18–23 months having the lowest (*Figure 3.5*). There was a clear reduction in notification rate corresponding with eligibility to receive each dose of the vaccine, with the greatest incremental decrease corresponding with eligibility to receive the second dose of the vaccine (*Figure 3.5*).

Figure 3.4. Pertussis notification rates in children aged under 2 years, by month of age, NSW, 1993–1999
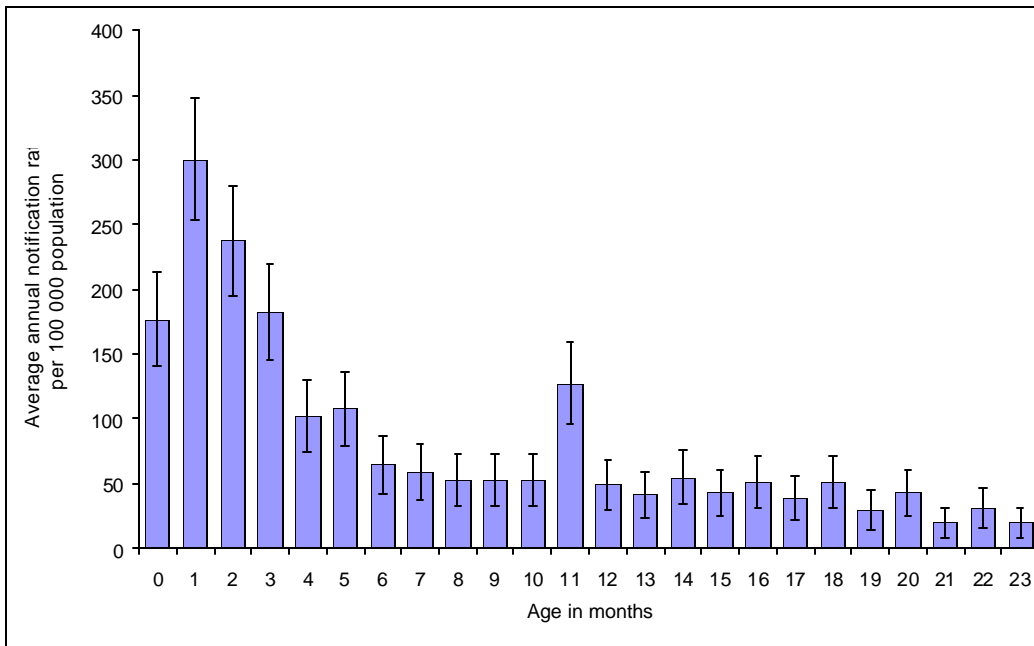
Figure 3.5. Pertussis notification rates in children aged under 2 years, by age group, NSW, 1993–1999
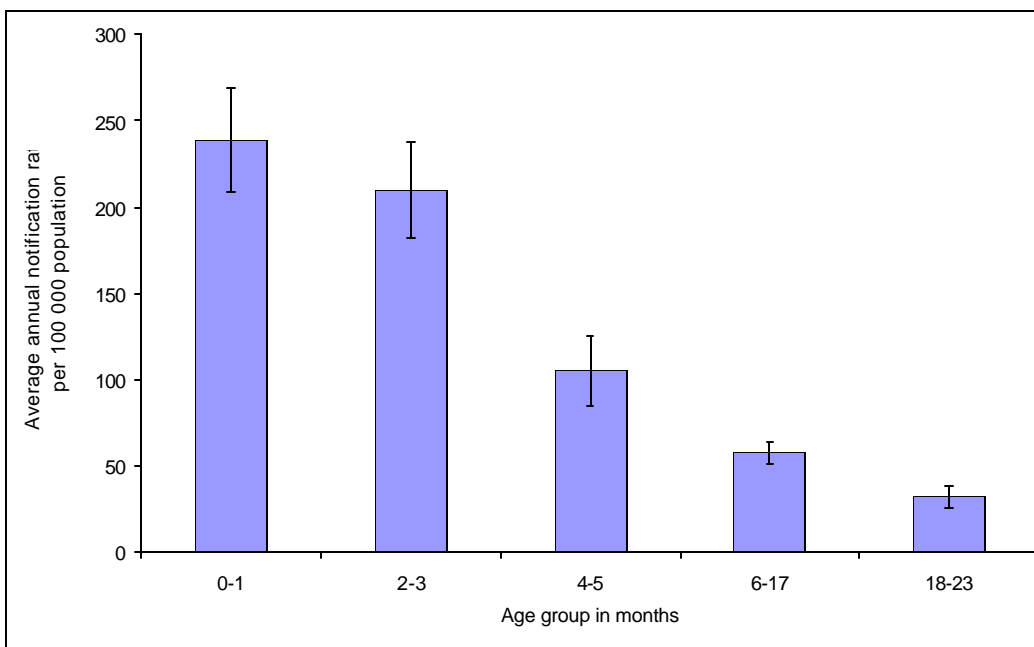
Children aged four months and over had a significantly lower risk of being notified with pertussis compared with infants aged less than two months. Risk decreased with increasing age (*Table 3.2*).

Table 3.2. Relative risk of pertussis notification by age group in children aged under 2 years, NSW, 1993–1999

Age group (months)	Doses eligible	Notifications	Estimated population	Relative Risk	95% CI
0-1	0	243	101 866	1.0 (referent)	-
2-3	1	214	101 866	0.88	0.73 to 1.06
4-5	2	107	101 866	0.44	0.35 to 0.55
6-17	3	351	611 196	0.24	0.20 to 0.28
18-23	4	99	305 598	0.14	0.11 to 0.17

The majority of cases aged less than two years, for whom information on the number of doses of a pertussis-containing vaccine was available, had not received any doses of a pertussis vaccine (*Figure 3.6*).

Figure 3.6. Pertussis notification rates in children aged under 2 years, by age group and number of doses of pertussis vaccine received, NSW, 1993–1999
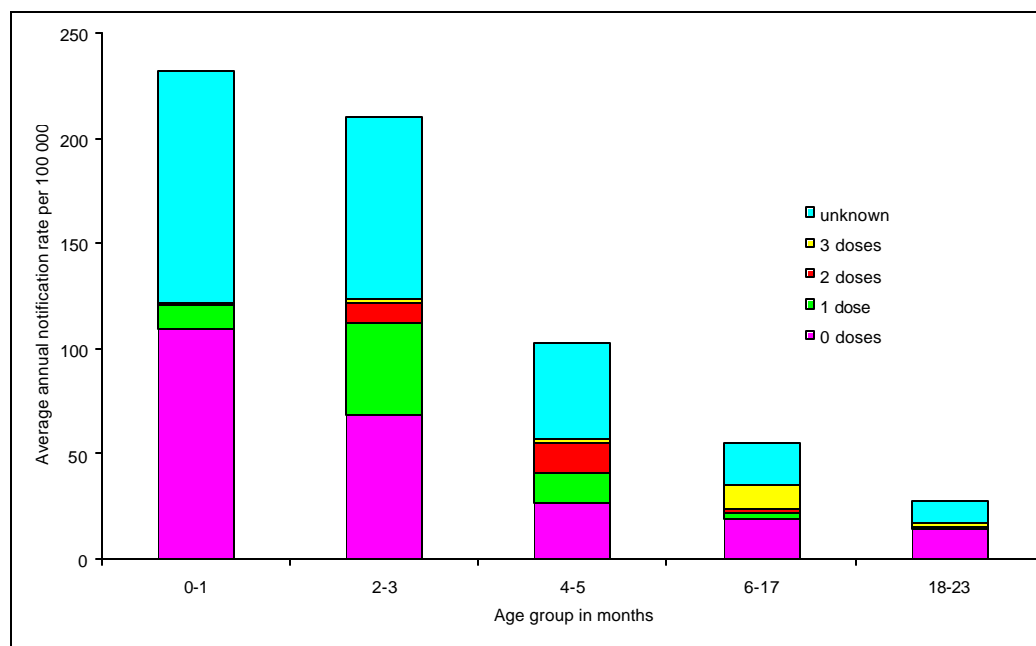
Method of diagnosis

Of the 13 456 notifications, 78% were coded as laboratory confirmed, 15% were coded as not laboratory confirmed and 7% had missing data (the NDD field was called 'LABCONF' and was a yes/no category). The method of diagnosis (the other NDD field relating to method of diagnosis which was called 'IDENMTHD') was either missing or coded as unknown in 3764 (28%) of cases. When data pertaining to laboratory confirmation were compared with data about the method of diagnosis (*Table 3.3*), a few anomalies became apparent. Of the 550 cases who were coded as diagnosed by culture, 50 (9%) were coded as not being laboratory confirmed (*Table 3.3*). Likewise, of the 7868 cases who were coded as diagnosed by serology, 330 (4%) were coded as not being laboratory confirmed.

Table 3.3. The NDD pertussis identification fields, NSW, 1993–1999

Method of Identification ('IDENMTHD')	Laboratory confirmed ('LABCONF')						
	missing	(%)	no	(%)	yes	(%)	Total
missing	21	(2.3)	321	(35)	564	(62)	906
unknown	772	(27)	661	(23)	1 425	(50)	2 858
clinical	124	(17)	572	(79)	26	(3.6)	722
serology	70	(0.9)	330	(4.2)	7 468	(95)	7 868
culture	4	(0.7)	50	(9.1)	496	(90)	550
PCR	0	(0.0)	1	(25)	3	(75)	4
antigen detected	0	(0.0)	16	(3.1)	505	(97)	521
microscopy	0	(0.0)	1	(4.3)	22	(96)	23
histopathology	0	(0.0)	1	(33)	2	(67)	3
radiologically active	0	(0.0)	0	(0.0)	1	(100)	1
Total	991	(7.4)	1 953	(15)	10 512	(78)	13 456

Note: The colours indicate the categories which were re-coded and correspond with the colours used in *Table 3.4* and *Figures 3.7, 3.11 & 3.12.*

After re-categorising the fields for method of diagnosis, 2782 (21%) of the cases had a missing or unknown method of diagnosis. Of the 10 674 cases for whom a method of

diagnosis was recorded, the majority (74%) were based on serology (*Table 3.4*). A further 16% of cases were diagnosed clinically, 5% based on culture results and the remaining 5% on 'other' methods.

Table 3.4. Method of pertussis diagnosis, after re-categorising, NSW, 1993–1999

Method of identification	n	(%)	% (of known)
clinical	1 704	13	16
serology	7 868	58	74
culture	550	4	5
PCR	4	0	0
other	548	4	5
Sub-total	10 674	79	100
Missing	793	6	
Unknown	1 989	15	
Total	13 456	100	

The categories radiologically active, histopathology, antigen detected and microscopy were re-categorised as 'other', and cases whose method of diagnosis was 'unknown' or missing *and* were recorded as not laboratory confirmed were re-categorised as 'clinical'.

During peak periods of pertussis notifications there was a rise in cases diagnosed by all methods, although the rise in notifications based on positive serology is the most obvious (*Figure 3.7*). The proportion of cases where the method was unknown or missing was highest in 1993 (44%) but has remained fairly constant from 1994–1999, averaging 19%. The proportion based on a positive serology has not significantly increased since 1994 (*Table 3.5* & *Figure 3.8*).

Figure 3.7. Pertussis notifications by method of diagnosis, for all ages, by month of onset, NSW, 1993–1999
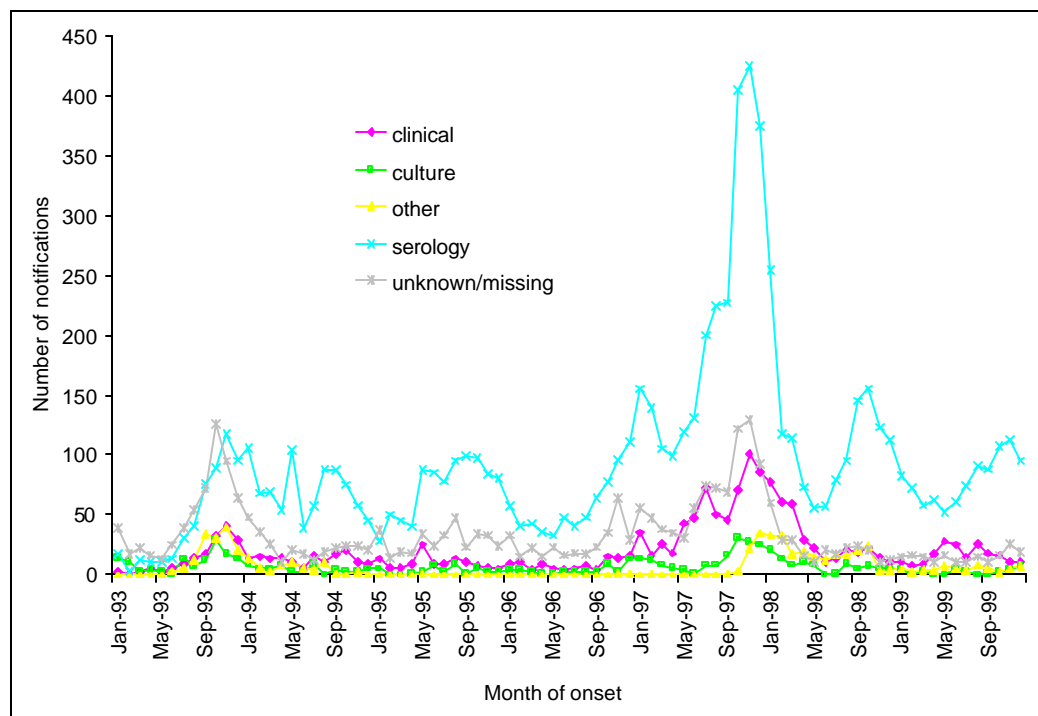
Table 3.5. Number and proportion of pertussis notifications based on positive serology, by year of onset, NSW, 1993–1999

Year	Number diagnosed by serology	Total (method of diagnosis known)	% serology	95% CI
1993	515	952	54	51 to 57
1994	850	1128	75	73 to 78
1995	869	1030	84	82 to 87
1996	695	847	82	79 to 85
1997	2604	3436	76	74 to 77
1998	1380	2043	68	66 to 70
1999	955	1238	77	75 to 79
Total	7868	10674	74	73 to 75

Figure 3.8. Proportion of pertussis notifications based on positive serology, by month of onset, NSW, 1993–1999
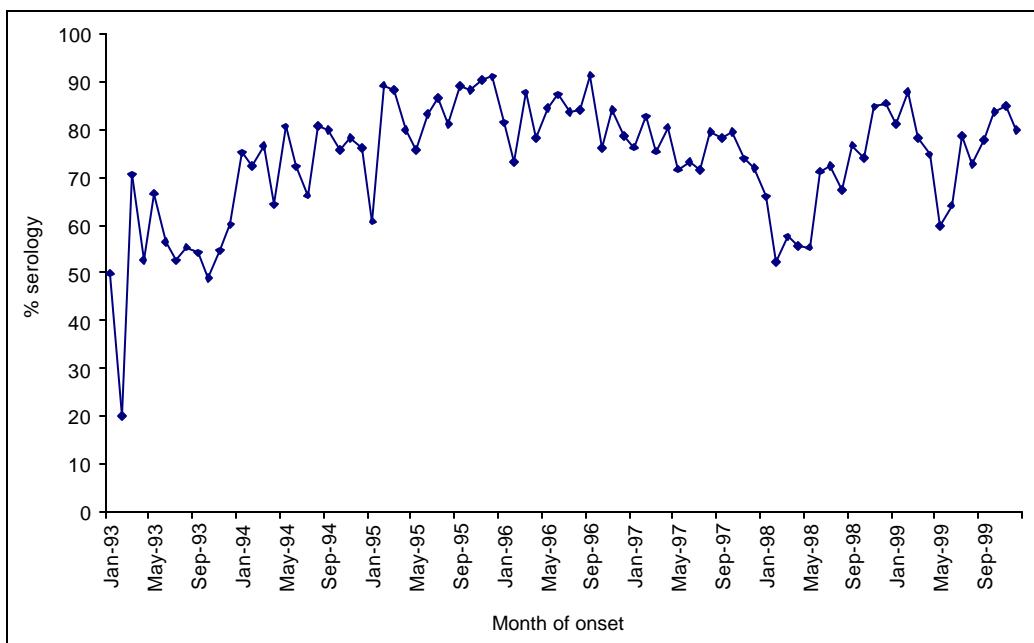
Serology had a much smaller impact on notifications in children aged under 5 years (*Figure 3.9*) than on notifications in persons aged 5 years and over (*Figure 3.10*).

Figure 3.9. Method of pertussis diagnosis by month of onset, 0 – 4 year olds, NSW, 1993 – 1999
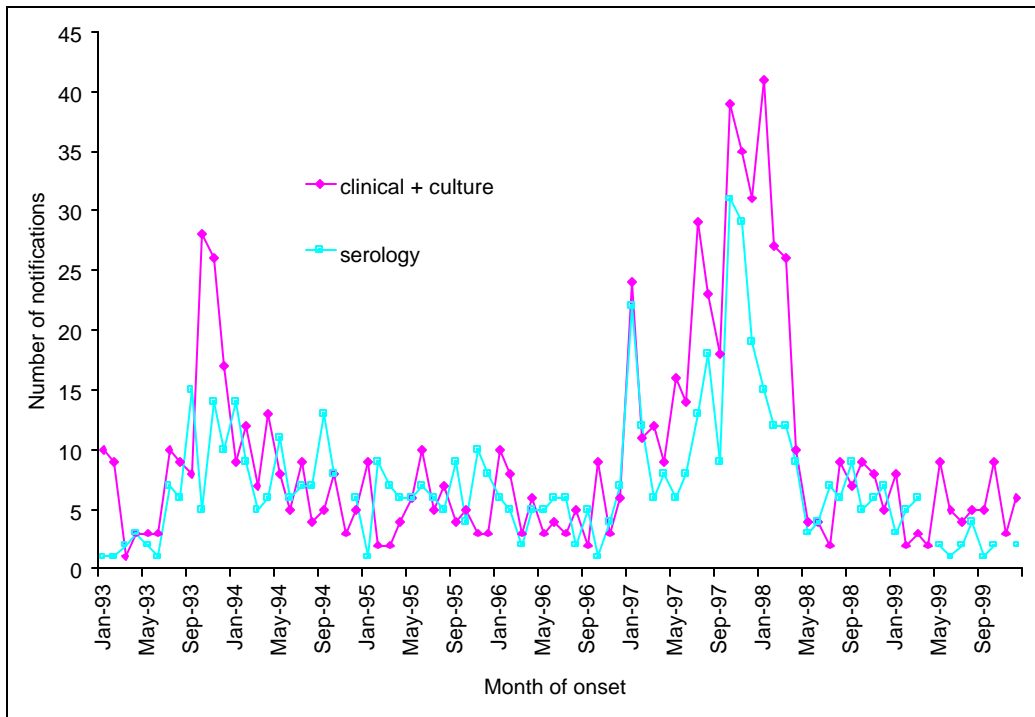
Figure 3.10. Method of pertussis diagnosis by month of onset, 5+ year olds, NSW, 1993 – 1999

73
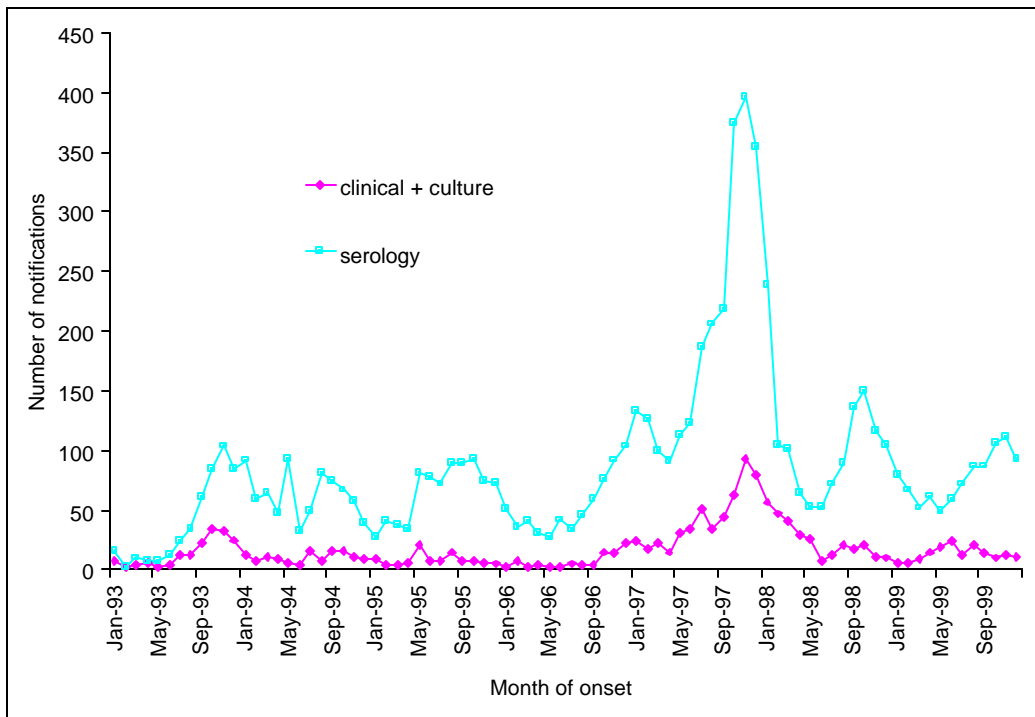
The proportion of notifications based on a positive culture result was greatest in infants aged less than one year, accounting for 25% of total notifications in this age group (including those whose method of diagnosis was unknown). This proportion decreased with increasing age, accounting for only 1% of cases aged 15 years or over. The proportion of notified cases aged less than one year who were hospitalised and diagnosed by culture was higher (34%) than all notified cases in this age group. Conversely, the proportion who were diagnosed by serology increased with age, ranging from 20% of cases aged less than one year to 66% of cases aged 15 and over (*Figure 3.11*). The proportion of notified hospitalised cases aged less than one year diagnosed by serology was slightly less than notifications overall (16%).

Figure 3.11. Method of pertussis diagnosis by age group, NSW, 1993–1999
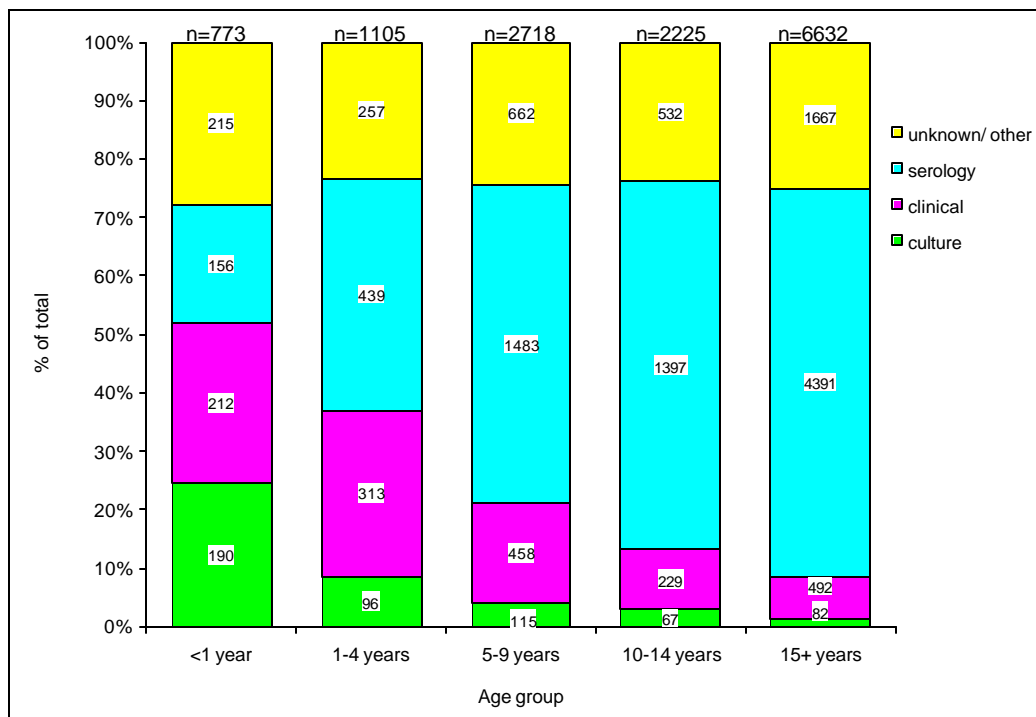
In children aged less than 24 months, the proportion diagnosed by culture was greatest among infants aged less than four months, with a trend for a decreasing proportion to be diagnosed by culture with increasing age ($\chi^2_1 = 40$, p<0.001). The proportion diagnosed by serology was greatest in those aged 18 months and over. The proportion of children aged under two years diagnosed clinically was similar in each age group (*Figure 3.12*).

Figure 3.12. Method of pertussis diagnosis by age group in children aged less than 2 years, NSW, 1993–1999
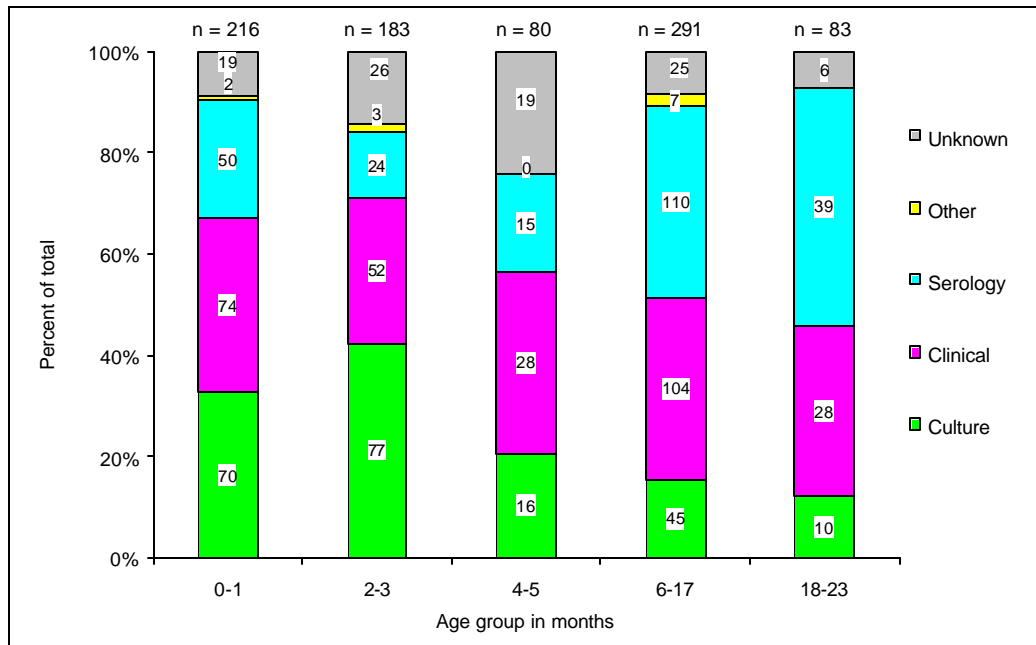
Geographic distribution

There was considerable variation in notification rates between the health areas, with Northern Rivers having the highest average annual notification rate and the Central Coast having the lowest (*Table 3.6*). In 12 of the 17 health areas, the highest notification rate was in 1997. Northern Rivers health area had a notification rate far exceeding that for other areas in 1994 and 1995, yet still had a high notification rate in 1997. In spite of being geographically adjacent to the Central Coast (*Figure 6.1*), since 1996 the Hunter region has had a much higher notification rate than this area. In 1997 the notification rate in the Hunter was over four times greater than that in the Central Coast.

Table 3.6. Pertussis notification rate per 100 000 population by health area and year of onset, NSW, 1993–1999

Area	1993	1994	1995	1996	1997	1998	1999	Average
Metropolitan								
Central Sydney	17.6	7.9	6.6	8.6	63.6	20.2	17.4	20.3
Northern Sydney	23.6	9.8	15.0	19.4	60.0	16.5	21.3	23.7
Western Sydney	20.1	20.8	19.9	23.3	81.9	24.5	14.3	29.3
Wentworth	26.7	22.6	40.7	22.5	99.0	61.7	17.9	41.9
S. Western Sydney	31.5	15.6	12.9	10.1	71.7	26.2	17.7	26.6
Central Coast	10.3	11.7	11.0	12.2	29.9	17.1	15.0	15.5
Hunter	11.6	13.8	15.5	27.4	127.2	48.4	52.3	42.7
Illawarra	17.1	24.5	29.9	10.2	56.3	65.1	16.8	31.6
S. Eastern Sydney	43.4	20.7	14.0	15.6	70.1	31.0	20.8	30.8
Total metropolitan	24.5	16.1	16.9	16.9	74.5	31.4	21.8	29.0
Rural								
Northern Rivers	49.4	190.6	122.8	25.0	70.1	23.1	5.8	68.2
Mid North Coast	24.3	26.8	23.4	21.7	46.9	43.2	18.2	29.3
New England	19.2	10.5	2.8	33.0	55.8	34.7	10.3	23.7
Macquarie	76.8	17.7	10.8	16.5	36.8	22.4	33.9	30.6
Mid Western	36.0	16.4	15.1	9.0	50.4	40.3	41.4	29.9
Far West	17.5	29.5	2.0	44.0	62.5	163.5	10.3	46.6
Greater Murray	2.0	9.8	48.9	30.4	26.4	90.1	35.0	34.7
Southern	4.1	17.2	25.5	14.5	52.8	41.0	26.9	26.2
Total rural	26.2	46.4	40.1	23.3	49.4	49.0	22.6	36.7
NSW total	25.5	23.2	22.3	18.5	69.2	35.4	22.0	31.0

Notifications in infants aged less than 12 months were examined by health area and financial year of onset to allow comparison with hospitalisation data (*Table 3.7*).

Table 3.7. Number of notifications and average annual rates per 100 000 population for infants aged less than 12 months by health area and financial year of onset, NSW, July 1993–June 1999

	93/94	94/95	95/96	96/97	97/98	98/99	Total	Average annual rate
Metropolitan								
Central Sydney	4	3	4	8	18	8	45	131
Northern Sydney	10	4	2	9	15	1	41	79
Western Sydney	15	10	13	14	27	7	86	144
Wentworth	3	3	2	11	14	5	38	124
S. Western Sydney	30	1	6	12	28	8	85	117
Central Coast	11	1	0	3	2	2	19	78
Hunter	15	6	16	11	26	7	81	181
Illawarra	5	4	2	3	12	2	28	97
S. Eastern Sydney	14	5	6	11	27	4	67	133
Total metropolitan	107	37	51	82	169	44	490	123
Rural								
Northern Rivers	28	20	11	0	13	2	74	364
Mid North Coast	12	3	7	4	11	10	47	233
New England	4	1	0	3	1	3	12	74
Macquarie	12	0	1	3	1	2	19	179
Mid Western	11	4	3	2	5	1	26	172
Far West	2	0	1	4	0	6	13	270
Greater Murray	0	5	5	4	2	4	20	82
Southern	2	3	3	2	4	2	16	102
Total rural	71	36	31	22	37	30	227	178
NSW total	178	73	82	104	206	74	717	137

The proportion of notifications which were laboratory confirmed was slightly greater in rural areas (87%) than in metropolitan areas (83%) (*Table 3.8*).

Table 3.8. Method of pertussis diagnosis by place of residence (rural versus metropolitan) and age group, NSW, 1993–1999

Age group (years)	Place	Culture %	Serology %	Other %	laboratory* %	Clinical %	Unknown %	n
0-4	Metro	22.8	38	2.9	64	36	22	1253
	Rural	13.0	48	1.1	63	37	27	613
5+	Metro	6.5	48	15.5	70	30	22	8442
	Rural	9.5	51	2.6	63	37	16	3051
Total	Metro	5.6	71	6.8	83	17	22	9695
	Rural	3.9	82	0.7	87	13	18	3664

* culture + serology + other

Hospitalisations

From July 1993 to June 2000, there were 1619 persons hospitalised with pertussis, giving an average annual hospitalisation rate of 3.7 per 100 000. Hospitalisation rates declined steeply with increasing age (*Table 3.9*). Children aged less than one year accounted for 61% of the hospitalisations and persons aged 15 years and over comprised only 9%. From July 1993 to June 1999 there were 955 hospitalisations in infants aged less than one year. In the same time period there were only 718 notifications in this age group, 291 of whom were recorded as being hospitalised.

Table 3.9. Pertussis hospitalisations by age group, NSW, July 1993–June 2000

Age group	Hospitalisations		Average annual
	n	%	rate per 100 000
<1 year	990	61	162.0
1-4 years	250	15	10.2
5-9 years	156	10	5.1
10–14 years	72	4	2.4
15+ years	151	9	0.4
Total	1619	100	3.7

Hospitalisation rates peaked in 1993/94 and again in 1997/98 (*Figure 3.13*).

Figure 3.13. Pertussis hospitalisation rates by age group and financial year of discharge, NSW, July 1993–June 2000
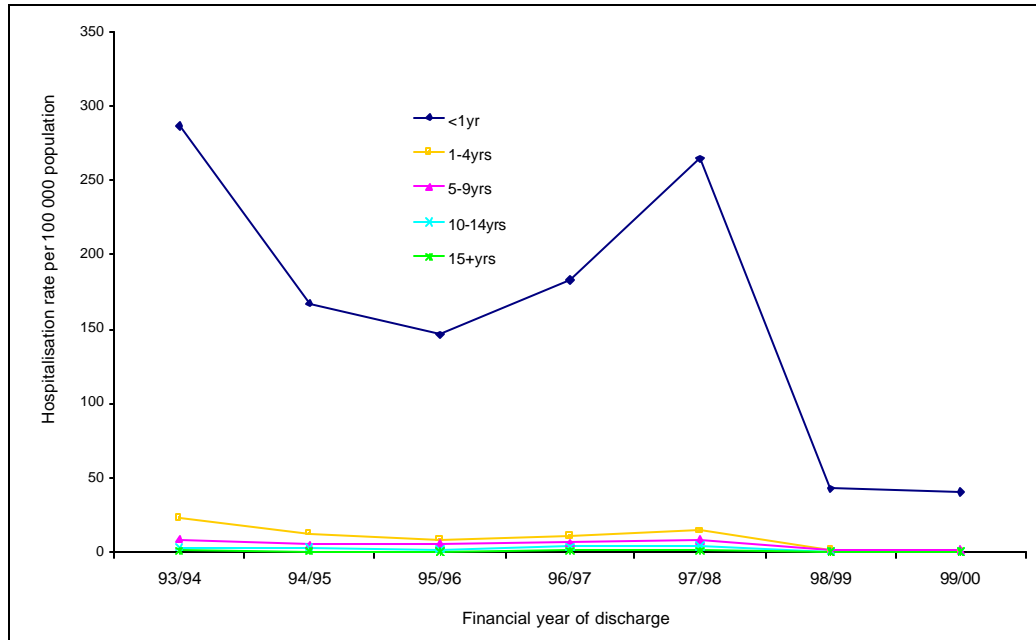
Children aged under 2 years

In children aged less than two years, hospitalisation rates were greatest in infants aged two months (*Figure 3.14*). In infants aged 3–7 months, there was a steep decline in hospitalisation rates with each month of increasing age. The greatest decrease was between infants aged two months and three months, followed closely by the decrease between infants aged three months and four months. From 7–23 months of age, hospitalisation rates remained at about the same level, decreasing slightly after 12 months of age. When the average annual hospitalisation rate in five age groups (corresponding with eligibility to receive 0, 1, 2, 3 & 4 doses of the vaccine) was examined in the same way as the notification data, infants aged two and three months had the highest rates and those aged 18–23 months had the lowest (*Figure 3.15*). The greatest incremental decrease in hospitalisation rates corresponded with eligibility to receive the second dose of the vaccine.

Figure 3.14. Average annual hospitalisation rates for pertussis in children aged under 2 years, by month of age, NSW, July 1993–June 2000
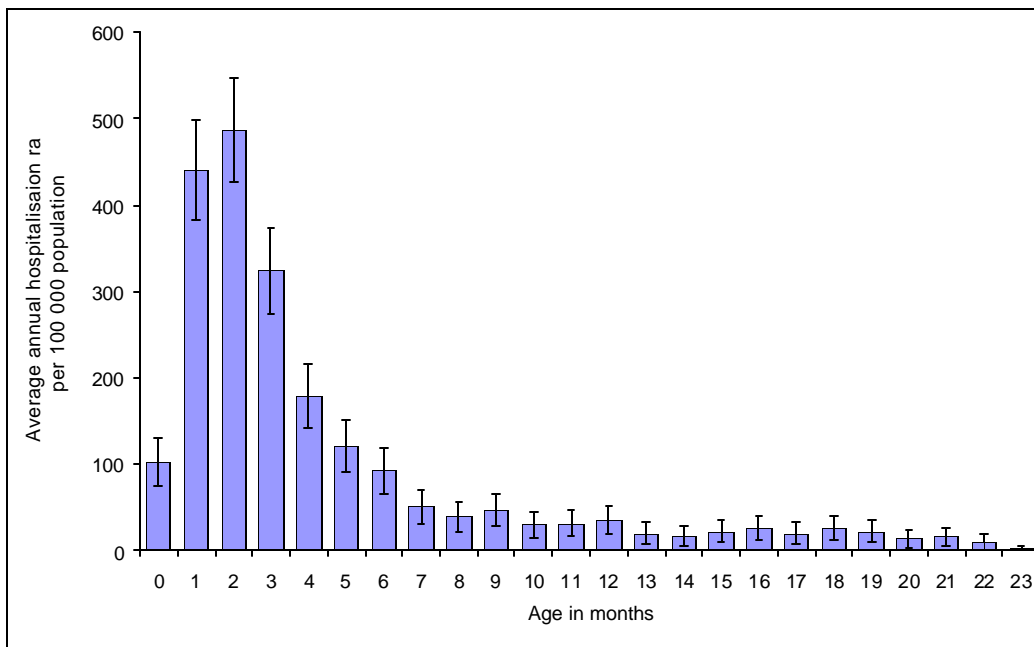
Figure 3.15. Average annual hospitalisation rates for pertussis in children aged under 2 years, NSW, by age group, July 1993–June 2000
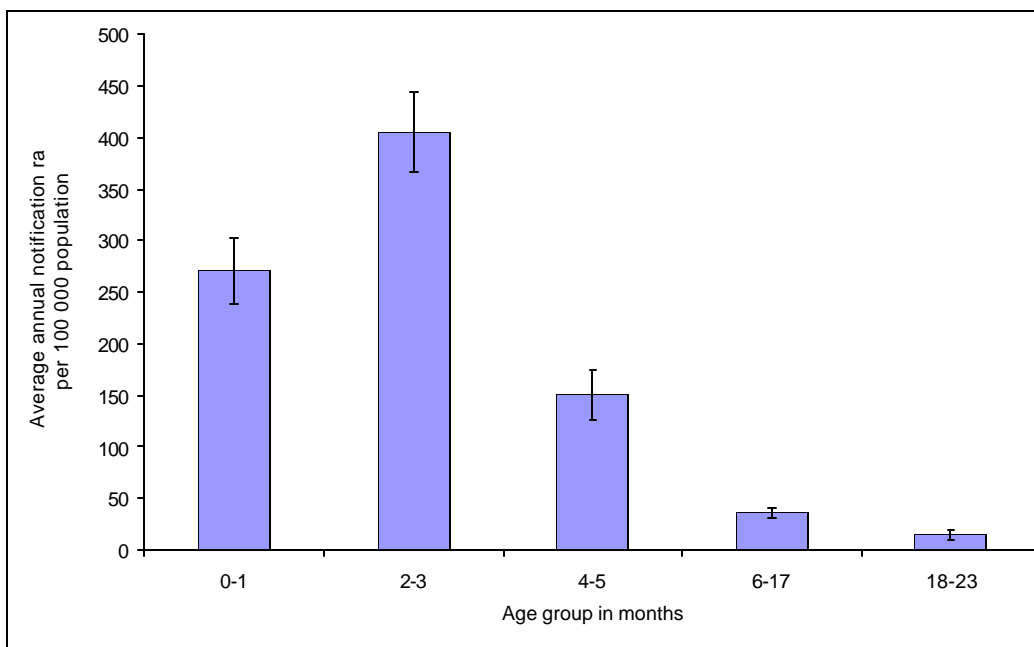
Children aged four months and over had a significantly lower risk of being hospitalised with pertussis compared with infants aged less than two months, and this risk decreased with increasing age (*Table 3.10*).

Table 3.10. Relative risk of pertussis hospitalisation by age group in children aged under 2 years, NSW, July 1993–June 2000

Age group (months)	Doses eligible	Hospitalisation	Estimated population	Relative Risk	95% CI
0–1	0	276	101 866	1.0 (referent)	-
2–3	1	413	101 866	1.50	1.29 to 1.74
4–5	2	153	101 866	0.55	0.46 to 0.68
6–17	3	219	611 196	0.13	0.11 to 0.16
18–23	4	45	305 598	0.05	0.04 to 0.07

Geographic distribution

Hospitalisation rates in infants aged less than 12 months varied between health areas (*Table 3.11*). Overall there were 949 hospitalisations between July 1993 and June 1999. This compares with only 717 notifications in the same time period (*Table 3.7*). The overall notification to hospitalisation ratio for the six-year period was 1:1.3, but varied by health area from 1:0.9 in the Hunter, Northern Rivers, Mid North Coast and Mid Western areas to 1:2.2 in South Western Sydney. For each of the metropolitan areas, except the Hunter, the total number of hospitalisations in this age group was greater than the number of notifications. This was also the case in half the rural areas. Unlike notification rates, the Hunter and Central Coast areas had similar hospitalisation rates.

Table 3.11. Pertussis hospitalisations and average annual rates per 100 000 population in infants aged less than 12 months by health area and financial year of separation, NSW, July 1993 – June 1999

Area	93/94	94/95	95/96	96/97	97/98	98/99	Total	Average annual rate	N:H* ratio
Metropolitan									
Central Sydney	15	5	7	9	14	6	56	163	1.2
Northern Sydney	12	5	5	9	17	6	54	104	1.3
Western Sydney	31	15	9	26	39	15	135	227	1.6
Wentworth	6	2	4	13	12	6	43	140	1.1
S. Western Sydney	52	17	19	34	51	14	187	258	2.2
Central Coast	16	9	0	2	5	3	35	144	1.8
Hunter	19	6	17	6	12	9	69	154	0.9
Illawarra	8	14	6	7	15	2	52	179	1.9
S. Eastern Sydney	13	9	5	10	24	6	67	133	1.0
Total metropolitan	172	82	72	116	189	67	698	176	1.4
Rural									
Northern Rivers	30	13	11	0	9	7	70	344	0.9
Mid North Coast	10	1	10	5	13	5	44	218	0.9
New England	3	0	0	4	7	2	16	98	1.3
Macquarie	17	4	1	6	1	2	31	292	1.6
Mid Western	8	8	3	1	3	1	24	159	0.9
Far West	15	2	1	0	1	1	20	416	1.5
Greater Murray	6	9	5	2	2	6	30	124	1.5
Southern	2	1	4	1	7	1	16	102	1.0
Total rural	91	38	35	19	43	25	251	197	1.1
NSW total	263	120	107	135	232	92	949	181	1.3

*Ratio of the total number of notifications to the total number of hospitalisations.

Discussion

Hospitalisations represent those pertussis cases with severe disease. However, it is difficult to know what type of cases those notified represent. The extent of under-notification is highlighted in the comparison of notification versus hospitalisation data in infants aged less than one year. The number of hospitalisations exceeded the number of notifications in this age group by 32%. This is the age group in which pertussis infection is the most severe and it is therefore targeted by pertussis control programs. In order to better control pertussis in this age group it would be useful to have a measure of incidence. Given that in this group the notification rate is even less than hospitalisation rate, it clearly underestimates incidence considerably. Hospitalisation data are less subject to variations in reporting practices than notification data (see *Limitations of the data*, Chapter 2) and may be more useful for monitoring trends in incidence in this age group than notification data.

Although pertussis is notifiable by law, a study undertaken in New South Wales in 1991 and 1992 (before and after the new *Public Health Act 1991*) found very little improvement in self-reported notification among general practitioners.[4] A study undertaken in the Northern Rivers Health Area in 1996 found that only 18% of notified pertussis cases had been notified by general practitioners.[5] A further study undertaken two years later, in 1998, in the South Eastern Sydney health area found that 40% of notified pertussis cases had been notified by general practitioners.[6] Although this is an improvement, it is still a low proportion. Reasons given by doctors for not notifying include the belief that the laboratory will notify, the extra time it takes to notify a case and poor knowledge of which diseases should be notified, of the notification process and of the role of the public health unit once the notification is received.[5,6]

Only one of the five deaths recorded in the Australian Bureau of Statistics Causes of Death Collection (see Chapter 2) was recorded in the NDD. This may be because the notification was received prior to the death of the infant and the information was not updated. Alternatively, the cases who died are likely to have been hospitalised cases, who may be less likely to be notified.

Age distribution

The age-specific notification rates for NSW follow a similar pattern to the national data (see Chapter 2). As NSW data are a large subset of the national data and there is a national vaccination schedule, this is to be expected.

The prime advantage of examining NSW data over national data is that age in months was available. The reduction in notification rate by age group, corresponding with eligibility to receive each dose of the vaccine, is suggestive of an impact of vaccination. Although other factors may play a role in this general decline in notification rate with age, it is unlikely that other factors could account for the pattern of the decrease. Younger infants may suffer from a more severe form of the disease, which could increase their chances of notification. Also, one may argue that older age groups are more likely to have suffered previous pertussis infections and so will be immune. However, based on notification and hospitalisation data, the number of infants infected with pertussis is small relative to the population, even allowing for under-reporting. Also, within each age group there was not always a decline in notifications by month of age. Instead there was a decrease in a stepwise fashion corresponding with eligibility to receive another dose of the vaccine. The pattern of the decrease is strongly suggestive of an effect of vaccination, with the second dose of the vaccine at four months of age having the greatest impact.

The percentage reduction in notification rates shown in *Table 3.1* could be regarded as a crude estimate of the effectiveness of the vaccination program at preventing notified cases of pertussis. The number of doses of vaccine received by cases in this age group suggest that only a minority had been age-appropriately vaccinated. Even without formal vaccine effectiveness estimations, the data suggest that most of the notifications in children aged less than two years are a result of failure to vaccinate or of being too young to be vaccinated, rather than vaccine failure. Likewise, the percentage reduction in hospitalisation rates shown in *Table 3.10* could be regarded as a crude estimate of the effectiveness of the vaccination program at preventing hospitalised cases of pertussis. Vaccine effectiveness is measured as one minus the relative risk, so the effectiveness of eligibility for the first two doses is 45% and for

three doses is 87%. Unfortunately the vaccination status of hospitalisations is not collected at the State level.

A similar pattern was observed in both hospitalisations and notifications by month of age for children aged less than two years, although some differences were apparent. The hospitalisation rate peaked in two-month-olds, not one-month-olds as was the case with notifications. However, in both notification and hospitalisation rates, one and two month olds had rates which were not significantly different from one other. The difference may be due to the date of admission occurring later than the date of onset, as the child may be less likely to require hospitalisation in the early catarrhal phase of the disease. It generally takes seven to ten days for the illness to enter the paroxysmal stage[7] where hospitalisation becomes more likely. There was a reduction in hospitalisation rate with each month of increasing age from two to seven months of age. Younger infants with pertussis are more likely to have severe disease which requires hospitalisation than are those who are older. However, the pattern of hospitalisations is still suggestive of an effect of vaccination, with the greatest impact coming from the second dose and a further significant reduction resulting from the third dose. Authors of a paper describing New Zealand surveillance data during an epidemic detected a similar pattern with the peak age-specific notification and hospitalisation rates in the six-week to two-month age group.[8]

Infants aged less than one month of age had significantly lower notification and hospitalisation rates than infants aged one month. This may be due to newborn infants having less exposure, having some protection from maternal antibodies or a combination of the two. Transplacental pertussis IgG antibody concentrations in newborns have been found to be comparable to maternal concentrations and to decline with a half-life of about six weeks.[9] However, the absolute quantities of antibodies were much lower than the concentrations seen after primary or booster pertussis vaccination.[9] The reason for a rise in notification rate in 11-month-olds is not clear. No similar rise was apparent in the hospitalisation rates, suggesting the result may be spurious or artefactual.

Method of diagnosis

Information on method of diagnosis was poorly collected over this time period. The reason that some of the notifications which were clearly based on a positive laboratory result were coded as 'not laboratory confirmed' is not clear. It may be that laboratory confirmation became available after the case had been notified, and the laboratory confirmation field was not updated. As laboratory confirmation can be derived from the method of identification field (assuming 'clinical' means clinical only), the other field seems to be redundant. The validity of the method of diagnosis data is not known. The category 'radiologically active' is presumably a data entry error and accounted for only one case. The assumption that cases whose method of diagnosis was 'unknown' or missing *and* were recorded as not laboratory confirmed were identified on clinical grounds may have resulted in some misclassification.

Culture was of most importance in infants aged less than one year and of least importance in adults. Culture of the organism from a nasopharyngeal swab or aspirate is the 'gold standard' for the diagnosis of pertussis. One study found that cultures gave positive results for the presence of *B. pertussis* in 75% of cases during the early coryzal stage of the disease.[10] However, during this early phase pertussis is less likely to be suspected and as the disease progresses it becomes increasingly difficult to culture the bacteria and by the whooping cough stage it is often not possible.[11] In most clinical situations the isolation rates are much lower.[12] A study in the Netherlands which used serology as the reference standard found the overall sensitivity of culture to be 7%, but that it varied considerably with the duration of disease at the time of diagnosis and with vaccination status.[11] The same study estimated the sensitivity of PCR as 21% but found that it declined with increasing age and increasing duration of disease.[11] Although only four notified cases were based on a positive PCR result, these were all in 1999 and the proportion may well increase in future years.

Overall, and particularly amongst persons aged more than 12 months, the majority of notifications were based on a positive serological result. This must be kept in mind when making international comparisons with countries such as the United States, whose case definitions do not include diagnosis by serology. As mentioned in the previous chapter, a study undertaken in western Sydney found that cases notified on

the basis of a widely used commercially available ELISA for IgA against whole-cell *B. pertussis* reported clinically consistent pertussis almost uniformly, suggesting that notifications based on positive serology underestimate, rather than overestimate, the true incidence of pertussis.[13] Authors of one review commented that, in symptomatic adolescents and adults, serology may be the most important diagnostic tool, since pertussis in these individuals is usually diagnosed late in the course of their disease and they are thus frequently culture negative.[14] There is no evidence from the notification data that the proportion of notifications based on serological tests has increased since 1994. However, it did increase from 1993 to 1994 and in South Australia the proportion of cases based on serology rose from 15% in 1985 to 90% in 1996.[1]

The proportion of notifications based on serology increased with age and the impact of serology on notifications was far greater in persons aged five years and over than it was in children aged less than five. This finding is not surprising, as infants aged less than one year have a less reliable IgA antibody response to *B. pertussis*[9] and the organism is more likely to be isolated from younger children.

The proportion of cases diagnosed clinically decreased with age. The case definition includes the presence of at least one typical pertussis symptom (paroxysms of coughing, inspiratory 'whoop' without other apparent causes or post-tussive vomiting) or is epidemiologically linked to a laboratory confirmed case. The decrease in clinically diagnosed cases with age is most likely due to the decline in typical pertussis symptoms with age and the increasing use of serology in older age groups. One study estimated that a clinical case definition of an acute cough lasting for 14 or more days had a sensitivity of between 84% and 92% and a specificity between 63% and 90% when used in an outbreak setting.[15] However, this case definition is of limited value in non-outbreak settings or when a case is not linked to a laboratory confirmed case. Some doctors are reluctant to notify a pertussis case without laboratory confirmation.[6]

When children aged less than two years were grouped according to eligibility to receive another dose of the vaccine, there was very little change in the proportions

notified with different diagnostic tests between age groups. This suggests that the decrease in notification rates with increasing age in children aged less than two years is unrelated to diagnostic testing.

Geographic distribution

The extent to which the differences in notification rates between areas reflect differences in incidence versus differences in diagnostic and notification practices is difficult to determine using notification data alone. However, the comparison of notifications and hospitalisations in the under-12-month age group in each area over the same time period provides some insights. The health area with the highest average annual notification rate, for all ages and for infants aged less than 12 months, was Northern Rivers. Northern Rivers also had the second highest hospitalisation rate (the highest was the Far West but this was calculated on very few cases) suggesting that pertussis incidence in this area is higher than in other areas. This is likely to be related to vaccination coverage. Northern Rivers has the lowest pertussis vaccination coverage of any NSW health area, with only 81% of children aged 12 months being recorded on the Australian Childhood Immunisation Register as having received three doses of a pertussis-containing vaccine in 1999 (see Chapter 4).

The Hunter had a much higher notification rate than the geographically adjacent Central Coast, with the average annual notification rate in infants aged less than 12 months in the Hunter being 230% higher than that in the Central Coast. In contrast, the average annual hospitalisation rate in this age group was only 7% higher in the Hunter. The most likely explanation for this is that the degree of under-reporting is greater in the Central Coast than in the Hunter. The ratios of notifications to hospitalisations for the health areas give an indication of the relative extent of under-reporting in each health area. Some health areas may more actively seek cases, particularly if they are experiencing an outbreak. Some of the differences in ratios may be due to doctors and/or laboratories in the area being more or less willing to notify. This may have more of an influence on notification rates in less densely populated areas where there are fewer doctors or laboratories.

Alternatively, it is possible that some areas with relatively low notification rates could have had relatively high hospitalisation rates if a greater proportion of disadvantaged

persons resided in that area. Perhaps infants who are malnourished or disadvantaged in some other way may be at greater risk of experiencing more severe disease than a well nourished, well cared for infant who is also infected with pertussis. This is speculation only and further studies would be required to determine whether this could be a plausible explanation.

The 1997/1998 pertussis epidemic affected most health areas and only two of the areas (Northern Rivers and Macquarie) had higher notification rates in years other than 1997 or 1998. Four of the five deaths recorded in the study period in NSW were in 1997,[16] suggesting that this increase in notification rate represents a true increase in pertussis incidence.

Conclusion

Even allowing for the limitations of data collected from a passive surveillance system, notification and hospitalisation data can provide much valuable information about the epidemiology of pertussis and the impact of vaccination programs. The hospitalisation data provide particularly useful information about pertussis in infants aged less than 12 months but less useful information about pertussis in older persons, amongst whom hospitalisation with pertussis is rare. Comparison of area-specific notification and hospitalisation data from the same time period can provide insights into the extent to which differences in notification data may reflect differences in pertussis incidence.

Pertussis remains an important public health problem in NSW with infants too young to be vaccinated having the greatest risk of death, hospitalisation and notification due to pertussis. The analysis of notification and hospitalisation rates by month of age shows a clear effect of vaccination, with infants eligible for two or more doses of pertussis-containing vaccine having a significantly reduced risk of being notified and/or hospitalised with pertussis. This risk is further reduced significantly with eligibility to receive the third and fourth dose of pertussis-containing vaccine. The reduction in notification rates over the time period amongst 5-9 year olds, together with the pattern of reduction within this age group, is strongly suggestive of an impact from the introduction of the fifth dose of DTP vaccine in late 1994. Overall, the results suggest that the vaccination program is effective for children aged less than 10

years. The effectiveness of the vaccination program is more formally assessed in Chapter 6.

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Chapter 4

The Australian Childhood Immunisation Register and pertussis vaccination

Background

A description of the epidemiology of any disease for which a vaccination program is in place requires a discussion of vaccination coverage. The Australian Childhood Immunisation Register (ACIR) is unique and its introduction in Australia in 1996 was the subject of much discussion, as well as criticism. This chapter provides a background to the development of the ACIR and then uses data from the ACIR to examine pertussis vaccine coverage and the number and type of vaccines administered, at both a national level and a State level for NSW. Some of the NSW vaccine coverage data presented in this chapter are used in the vaccine effectiveness estimations (Chapter 6).

The ACIR data were kindly provided by Brynley Hull. The DTP coverage figures for Australia and NSW at 12 and 24 months of ages (*Figures 4.2, 4.3, 4.12 & 4.13*) are those published quarterly in *Communicable Diseases Intelligence*.

Immunisation registers and development of the Australian Childhood Immunisation Register (ACIR)

Public health registers

Last[1] defines a register as a file of data concerning all cases of a particular disease or other health-related condition in a defined population such that the cases can be related to a population base. The register is the actual document, and the registry is the system of ongoing registration.[1] For epidemiologic purposes population-based registers are generally considered to be the most useful.[1,2] For example, in cases where the register records disease, incidence rates may be calculated. Similarly, where the register records immunisations, coverage rates may be calculated. Public health registers are population based rather than hospital or clinic based.

Public health registers may be based on the collection of cases of disease or events, or on persons.[3] Registers which are based on cases or events require population census data in order to calculate rates whereas those which are person based hold their own denominator data.[3] Person-based registries are less common than disease registries.[3] Reasons for this include concerns about privacy and confidentiality, the difficulty of

handling such large data sets and the comparatively recent recognition of the need for such registers.[3]

The most successful registries are those in which purposes are explicit and realistic, the data collected are accurate and are limited to essential information, and the registry meets needs that cannot be accommodated using simpler, less expensive methods. The complexity of the data-collection process limits the extent to which data can be made rapidly available.[2]

Immunisation registers

General characteristics of an ideal immunisation register include: being population based; the inclusion of *all* children regardless of nationality and residency status, or any other characteristic; the ability to produce aggregate statistics and individual information in a timely manner; a high level of accuracy and completeness; a core data set including a unique personal identifier; the capacity to deliver both aggregate data on immunisation coverage and individual immunisation status information, including a recall/reminder service at parental and health service levels; the capacity to deliver profiles of immunisation providers, classes of providers, and vaccine consumption by region and trends over time; and financial and organisational efficiency.[3,4] Specific characteristics of an ideal register include the provision of: regular and accurate immunisation coverage data for particular ages by vaccine type and area of residence; timely recall/reminder notices to parents; accurate information for parents on the immunisation status of their child, including official certification; accurate information to providers on the immunisation status of particular children who attend for immunisation, including opportunistic immunisation; accurate information on unimmunised or incompletely immunised children to health departments and providers; profiles of immunisation providers by region, and trends over time; vaccine consumption by type for different regions and trends over time.[3] In addition, an ideal register might be able to be linked with infectious disease notifications or adverse events for the purpose of estimating vaccine efficacy and increasing information on vaccine side effects.[3] The recording of a batch number may allow the estimation of vaccine efficacy and the collection of side effect information by vaccine batch.[3] If demographic information such as ethnic group is collected then

this allows the reporting of immunisation coverage by group.[3] Otherwise demographic categories must be inferred from area of residence by proxy variables.

Prior to the advent of the Australian Childhood Immunisation Register (ACIR) there were two types of population-based immunisation registers in Australia, those operated by municipal councils, especially in Victoria, and the reminder system operated in the Australian Capital Territory (ACT).[3] The Support and Evaluation Resource Unit[5] describes the operation of such population based registries as patchy and as varying across States and Territories. Problems with local registers are mainly related to incomplete information on all children, as families move in and out of areas.

In addition, there are provider-based reminder systems operated by many general practitioners throughout Australia.[3] The main limitations of these are that they are generally not population based and as such cannot provide coverage data. Few general practitioners have formal reminder systems.[35]

Queensland has continued to operate a separate register, the Vaccine Information and Vaccine Administration Service (VIVAS), which commenced before the ACIR. VIVAS, a centralised system of vaccine supply which includes delivery coupled with reporting,[3] has the potential to link communicable disease notifications and adverse events reports to the immunisation record of individual children and particular vaccine batches. This would be ideal for estimation of vaccine effectiveness.[3] The system in the ACT is also one whereby general practitioners are given free vaccines in exchange for provision of vaccination data to ACT Health. [6]

The ACIR

Overseas experience has shown that registers help to improve immunisation rates by reminding parents and providers and by providing information on immunisation coverage to help public health managers target programs.[4] As a result of the inadequacies with existing registries, difficulty in coordination across jurisdictional boundaries and the success of population-based immunisation registers in immunisation programs in other developed countries,[3] the ACIR was developed.

The ACIR is one element of a national strategy to improve and maintain high immunisation coverage in Australian children under the age of seven years.[3] The broad objectives of the ACIR were:

- to form the basis for a recall/reminder scheme which will inform parents when their child's next vaccination is due;

- to enable parents and immunisation providers to check on the immunisation status of an individual child regardless of where the child was immunised; and

- to provide a measure of immunisation coverage data at national, State/Territory and local levels.[7]

The ACIR is administered by the Health Insurance Commission (HIC) as part of the National Childhood Immunisation Program.[3] The ACIR commenced on January 1, 1996. On this day, all children of eligible age for the register (ie, less than seven years of age) had their details copied from Medicare (Australia's universal health insurance scheme) to the ACIR. The Medicare database constitutes an almost complete population denominator, as approximately 98% of children are estimated to be registered with Medicare by 12 months of age.[8] All children on the ACIR have an end date which coincides with their seventh birthday. All children born since 1 January 1996, who are enrolled with Medicare, are recorded on the ACIR by way of daily transfers from Medicare files.[3] In addition, if a child is not enrolled in Medicare, he or she can be added to the ACIR when details of an immunisation are supplied by a provider. Children who have died, moved abroad or been removed from Medicare are allocated an end date which coincides with their death or departure. Only immunisations given since 1 January 1996 have been entered onto the ACIR. As a result, ACIR data are less complete for children with birth dates prior to 1 January 1996. Monetary incentives for notification of immunisation encounters to the register are used to encourage provider participation.[5]

Information

Immunisations are notified to the HIC by either electronic means or by paper ACIR notification forms, which are scanned electronically and checked in Perth before transmission to the HIC central office in Canberra.[8] Notifications which are not in accordance with the National Health and Medical Research Council (NHMRC)

guidelines, or are duplicates, are queried with the provider and if their validity cannot be established they are rejected.[8]

The following information is collected by the ACIR.

Child

Child information may include: parent/guardian name, child surname, given name, address, date of birth, gender, aboriginality, Medicare number, vaccines administered by type and dose, date of service and service provider details.[9]

Provider

Service provider information may include: surname, given name, initial, address, phone number, provider/registration number, date of birth, bank account details, payment details and immunisation services provided.[9]

Vaccines

The vaccines recorded on the ACIR are those on the NHMRC's schedule for children from birth to six years of age.[9]

The flow of information to and from the ACIR is summarised in *Figure 4.1.*

Figure 4.1. Flow of information to and from the ACIR
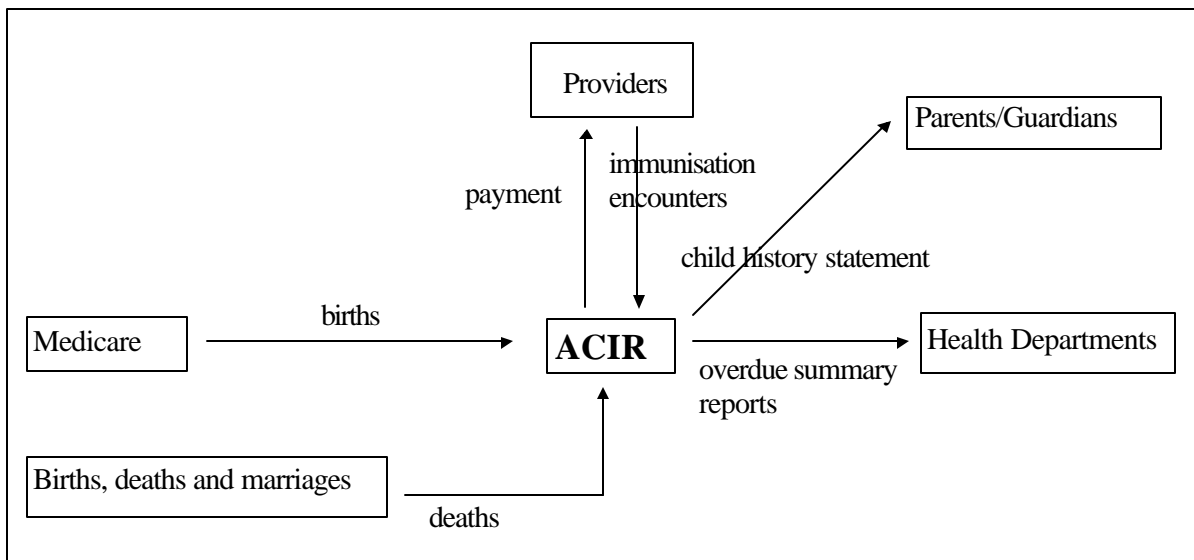
Calculating population vaccination coverage data

Population coverage figures are calculated from the ACIR data using the cohort method. A three month cohort of children is defined by date of birth, the first cohort being born between 1 January 1996 and 31 March 1996.[8] At the 12-month assessment date of 31 March 1997, this cohort was aged 12 months to less than 15 months, although only vaccinations given on or before the child's first birthday were considered.[10] If a record indicates that a child has received the third dose of a vaccine, then they are assumed to have received the two earlier doses, even if records of the previous doses are missing.[11] The immunisation status of members of each cohort at 12 and 24 months of age is published quarterly in *Communicable Diseases Intelligence.* Reports include the percentage of all children registered on the ACIR who are immunised according to the schedule for each disease at the time of assessment. The cohort method is also used to assess immunisation coverage in the United Kingdom and by countries reporting to the World Health Organization (WHO), thus allowing for international comparisons.[8]

Data quality

The data quality of any large database has three main components — currency, accuracy and comprehensiveness.[3] The data currency of the ACIR has improved progressively since its commencement[3] and it is expected that all aspects of data quality will improve with time. Major factors leading to poor data quality are related to vaccine providers either not reporting to the ACIR or reporting encounters in a non-timely fashion. A re-evaluation of the ACIR coverage estimates for three of the early birth cohorts using 1999 data found that the earlier coverage estimates had underestimated 'true' coverage by at least 2-4%.[12]

In July 1998, several schemes were introduced to improve the completeness and timeliness of reporting immunisation encounters to the register. These included the General Practice Immunisation Incentives (GPII) Scheme, whereby general practitioners received a service incentive payment of $18.50 for each encounter form received by the HIC, plus an outcome bonus payment if they reached target levels of immunisation coverage.[13] This was in addition to the standard $6 received by all immunisation providers for receipt of an immunisation encounter form. Parental incentives were also introduced and were linked with maternity allowance, childcare

assistance and childcare rebate.[13] Full payment of these allowances to parents was dependent upon their child being recorded as fully immunised on the ACIR or their having signed a form to state that they were conscientious objectors to immunisation. A second evaluation of the ACIR, undertaken in late 1999, concluded that the ACIR data quality had improved considerably since the first evaluation of the Register in 1997, and that the immunisation incentives offered to general practitioners under the GPII Scheme had had a positive influence on reporting behaviour and subsequent data quality.[14] However, it is believed that immunisation coverage estimates from the ACIR still under-estimate the 'true' level of coverage. A study aiming to measure the difference in immunisation rates reported by parents compared with that documented in the ACIR and to assess the level of under-reporting to the ACIR by providers, will be undertaken by staff at the National Centre for Immunisation Research in the second half of 2001.

The remainder of this chapter uses data from the ACIR to describe pertussis vaccine coverage and trends in the types of vaccine used.

Using data from the ACIR: Pertussis vaccination in Australia

Coverage

Changes in pertussis vaccine coverage can have a dramatic effect on pertussis notifications (see Chapter 1). It is important to be able to measure coverage as part of a disease control strategy. Prior to the implementation of the ACIR, vaccination coverage estimates were derived from a variety of sources.[15] The only national surveys that can be generalised to the whole population are the Australian Bureau of Statistics (ABS) household surveys, the most recent of which was conducted in 1995.[16] The ABS survey results are derived from a cross-sectional sample of children aged 12-23 months, hence these rates are not directly comparable with those from the ACIR.[16]

The proportion of children aged 12 months recorded on the ACIR as having received 3 doses of DTP ranged from 77% in March 1997 (the first birth cohort) to 92% by December 2000 (*Figure 4.2*). From December 1999 to December 2000, coverage remained at around 90%. This increase is probably due more to increased notification

to the ACIR than to any increase in vaccination coverage over this period.[17] The ABS 1995 survey estimated coverage at 86%.[16]

The proportion of children aged 24 months recorded on the ACIR as having received 4 doses of a diphtheria-tetanus-pertussis vaccine (DTP) was only marginally lower and ranged from 76% in March 1998 (the first birth cohort) to 90% by December 2000 (*Figure 4.3*). This suggests that most children who receive the first three doses will also receive the fourth dose.

Figure 4.2. DTP coverage (dose 3) at 12 months of age, by birth cohort, Australia, March 1997–December 2000
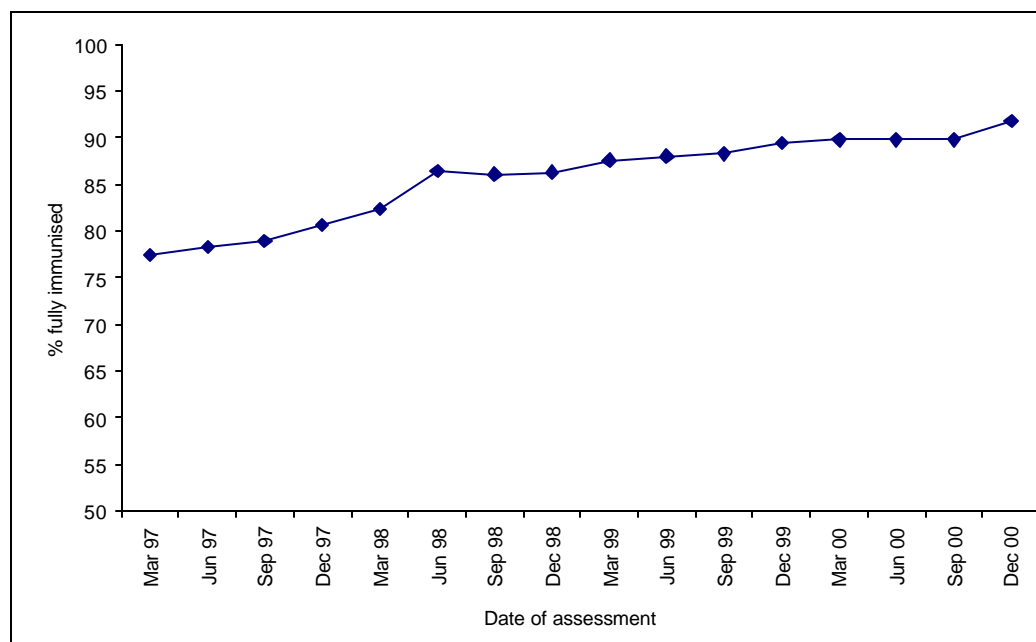
Figure 4.3. DTP coverage (dose 4) at 24 months of age, by birth cohort, Australia, March 1998–December 2000
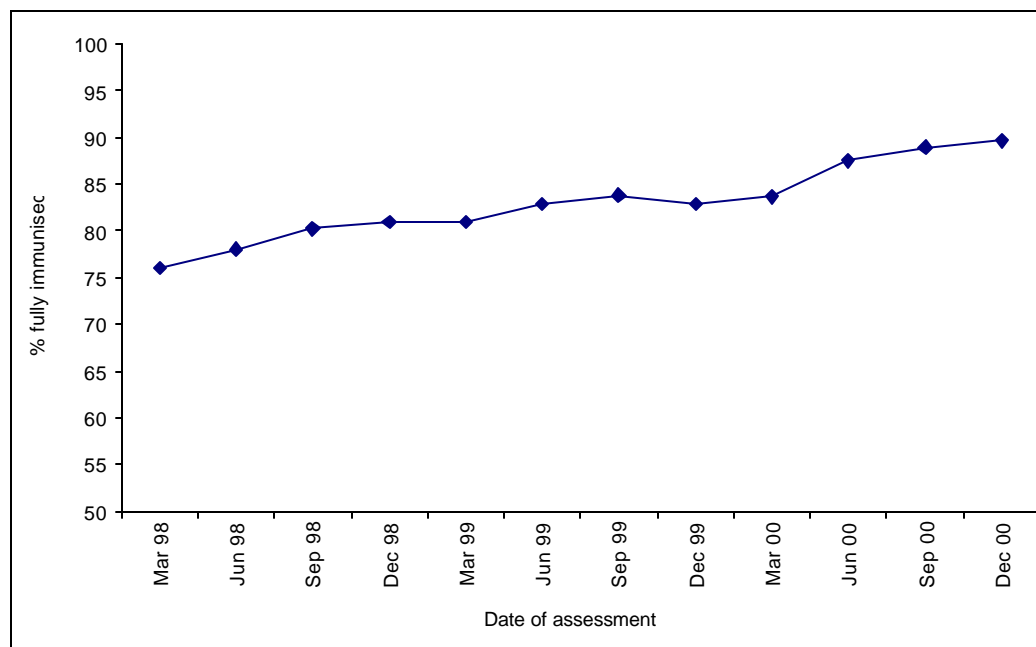
Trends in pertussis vaccine use

Where more than one type of vaccine is licensed, the ACIR records the vaccine type. Such is the case with pertussis vaccines since an acellular pertussis vaccine (DTPa) was licensed for use in Australia in 1997. In this section, data from the ACIR were used to track changes in pertussis vaccine use at a national level. This is the first time that data from the ACIR have been used for this purpose.

Since early 1997 the use of the acellular pertussis vaccine (DTPa) increased, with a corresponding decrease in the use of whole-cell vaccine (DTPw) (*Figures 4.4–4.6*). There was a steep increase in the use of DTPa in the primary course during 1999, and by April 1999 the number of DTPa vaccines given in the first three doses exceeded the number of DTPw vaccines (*Figure 4.4*). Prior to 1999, DTPa was available free of charge for the first three doses only in South Australia and the Northern Territory. In 1999, DTPa became available free of charge in all States and Territories. By August 2000, only 3% of DTP vaccines given as part of the primary course were recorded as whole-cell vaccines.

Figure 4.4. Number of doses of DTPw and DTPa (doses 1-3) administered each month, Australia, January 1996–August 2000
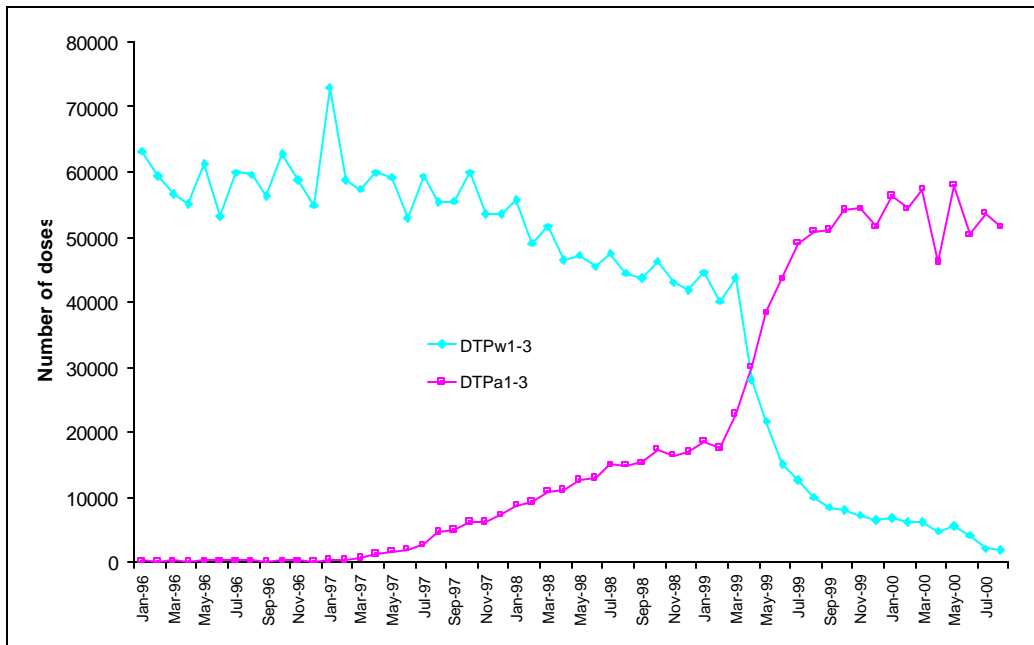
The number of acellular vaccines given as a fourth or fifth dose exceeded the number of whole-cell vaccines given for these doses since March 1998 (*Figure 4.5*). DTPa has been funded at the national level for the fourth (18 month) and fifth (preschool) boosters since 1997. The number of DTP vaccines given as a fourth or fifth dose peaked in January each year, coinciding with the timing of the preschool fifth dose. By August 2000, only 3% of DTP vaccines given as booster doses were whole-cell vaccines.

Figure 4.5. Number of doses of DTPw and DTPa (doses 4–5) administered each month, Australia, January 1996–August 2000
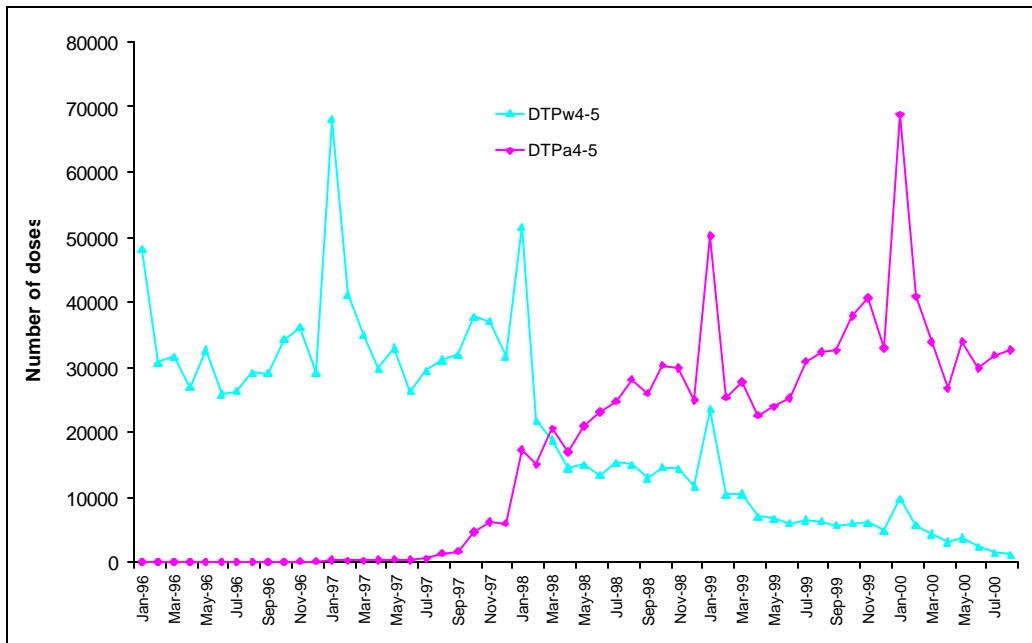
Combined diphtheria-tetanus vaccine (CDT) has not been a part of the routine immunisation schedule since 1994, when it was replaced by the preschool booster dose of DTP. It is only recommended where DTP is contraindicated. The number of doses of CDT vaccines administered is negligible compared with the number of DTP vaccines (*Figure 4.6*). Since acellular vaccines became available, the number of CDT vaccines used was greatly reduced (*Figure 4.7*). Of all the CDT vaccines administered in the time period examined, 30% were given as a preschool booster dose. The reduction in the number of CDT vaccines given each year in January, particularly CDT5, suggest that, although CDT use as the preschool booster continued well beyond 1994, its use decreased each year. By January 2000, only 173 doses of CDT5 were recorded. The decrease in CDT use could be at least partly due to parents and providers who were concerned about vaccine side effects being more willing to have their child vaccinated with an acellular vaccine. Since March 2000, fewer than 100 CDT vaccines per month were recorded on the ACIR as having been given, suggesting that this vaccine is not being inappropriately used.

Figure 4.6. Number of doses of DTPw, DTPa and CDT (doses 1–5) administered by month, Australia, January 1996–August 2000
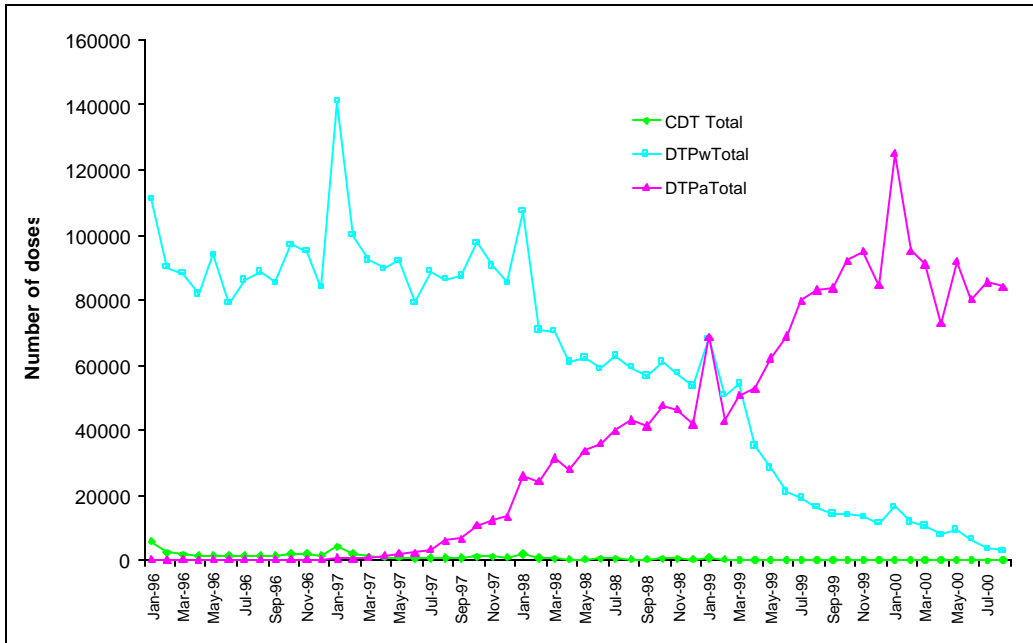
Figure 4.7. Number of doses of CDT (doses 1–5) administered by month, Australia, January 1996–August 2000
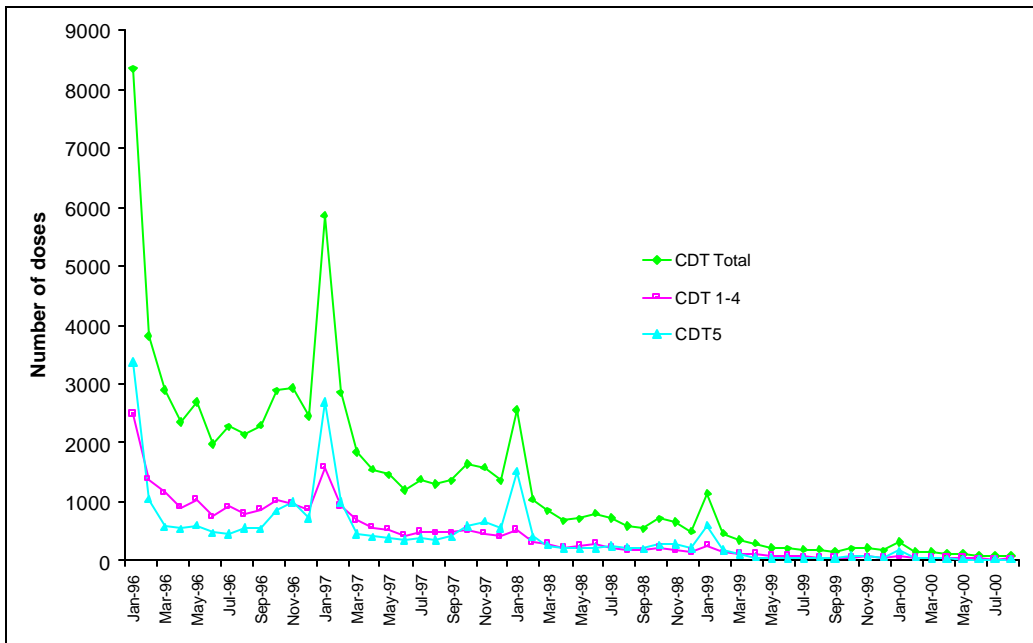
Using data from the ACIR:
pertussis vaccination in New South Wales

Trends in pertussis vaccine use

In this section, trends in vaccine use are examined in the same way as the national data in order to assist with interpretation of NSW notification data. Patterns of use of whole-cell and acellular vaccines for the first three doses were very similar to the national trends, with the number of acellular vaccines administered exceeding the number of whole-cell vaccines since May 1999 (*Figure 4.8*). Widespread use of acellular vaccines for the fourth and fifth doses occurred slightly later in NSW compared with the national pattern, with the number of acellular vaccines not exceeding the number of whole-cell vaccines until September 1998 (*Figure 4.9*).

Figure 4.8. Number of doses of DTPw and DTPa (doses 1–3) administered by month, NSW, January 1996–August 2000
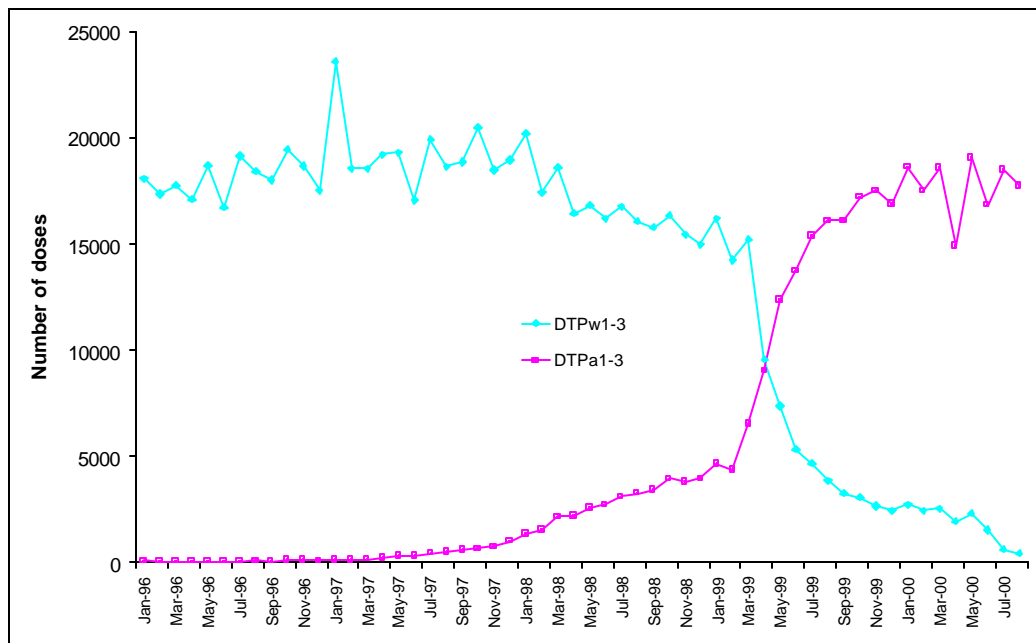
Figure 4.9. Number of doses of DTPw and DTPa (doses 4–5) administered by month, NSW, January 1996–August 2000
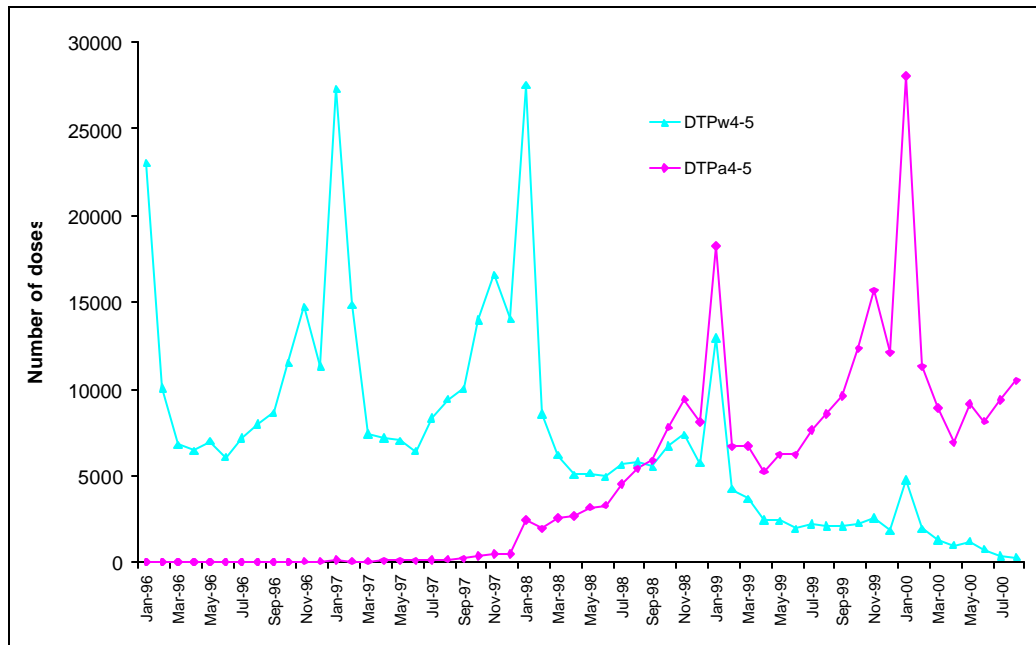
Of all the CDT vaccines administered in the time period examined, 46% were given as a preschool booster dose, a greater proportion than at the national level.

Figure 4.10. Number of doses of DTPw, DTPa and CDT (doses 1–5) administered by month, NSW, January 1996–August 2000
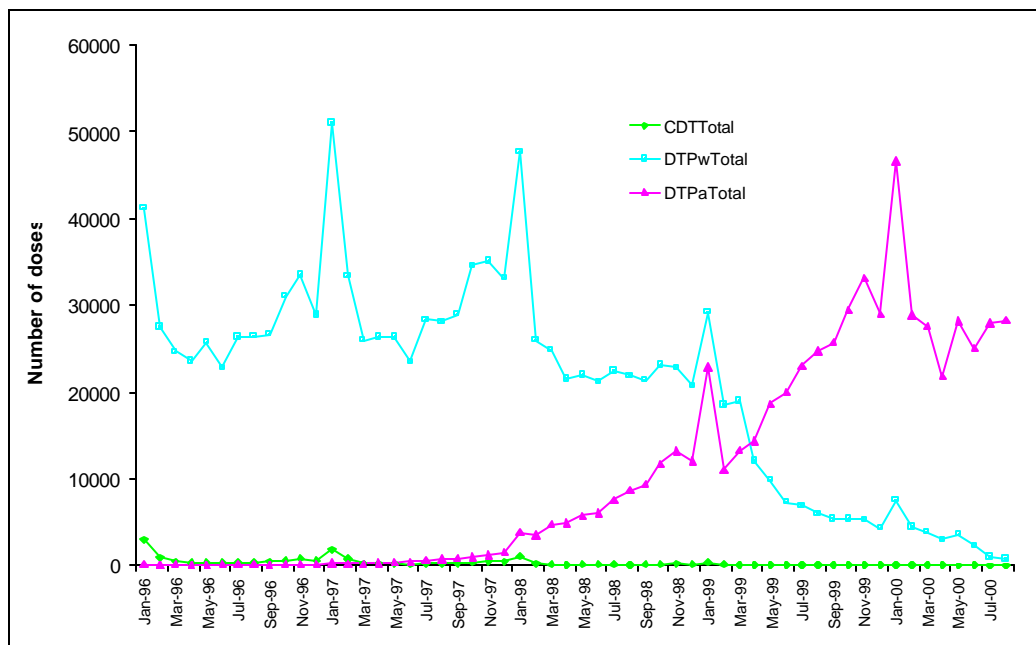
Figure 4.11. Number of doses of CDT (doses 1–5) administered by month, NSW, January 1996–August 2000
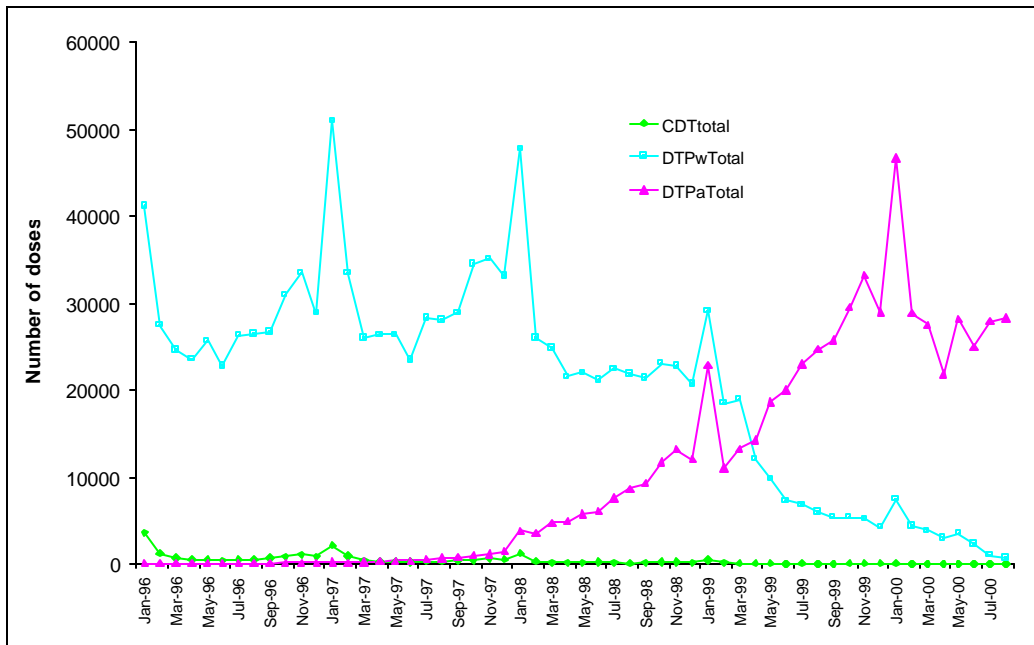
Pertussis vaccine coverage

The proportion of NSW children aged 12 months recorded on the ACIR as having received 3 doses of DTP ranged from 75% in March 1997 (the first birth cohort) to 91% by December 2000 (*Figure 4.12*). From December 1999 to September 2000, coverage remained at around 88% and then rose to 91% in December 2000. Although the earlier figures were lower than the national figures, by December 2000, NSW coverage was similar to the national coverage. A 1997 study involving a random sample of 850 NSW children identified by the ACIR as 90 days overdue for at least one scheduled immunisation found that 85% of these children were in fact fully immunised.[18] Hence the increase in coverage was probably due more to increased notification to the ACIR than to any increase in vaccination coverage over this period.

Figure 4.12. DTP coverage (doses 1–3) at 12 months of age, by birth cohort, NSW, March 1997–December 2000
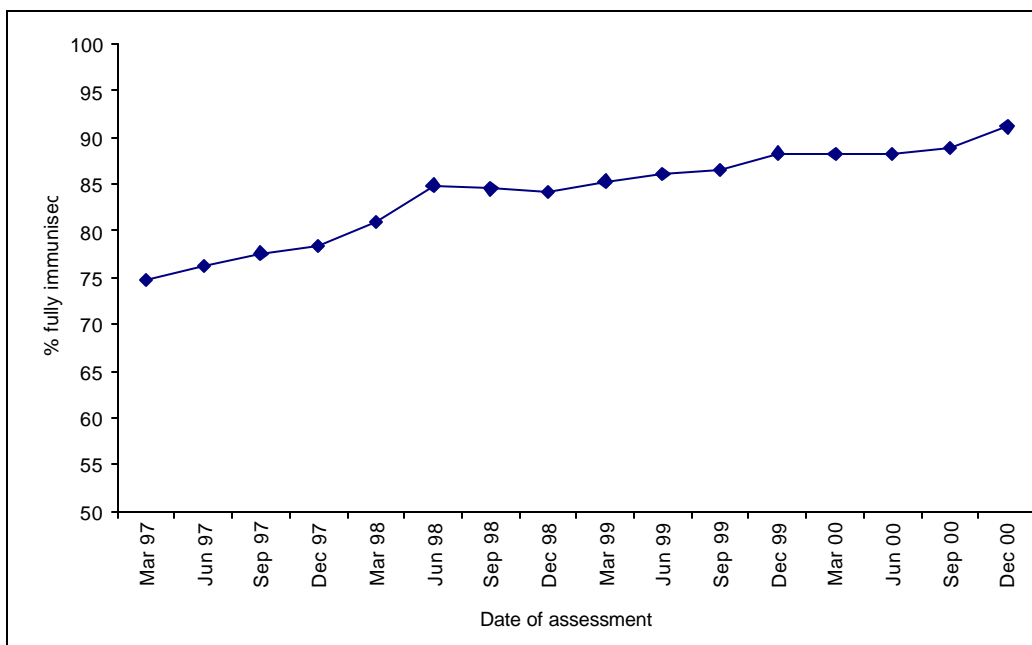
The proportion of children aged 24 months recorded on the ACIR as having received 4 doses of a diphtheria-tetanus-pertussis vaccine (DTP) was only marginally lower and ranged from 76% in March 1998 (the first birth cohort) to 88% by December 2000 (*Figure 4.13*). These figures are similar to the national ones and suggest that most NSW children who receive the first three doses will also receive the fourth dose.

Figure 4.13. DTP coverage (dose 4) at 24 months of age, by birth cohort, NSW,
March 1998–December 2000
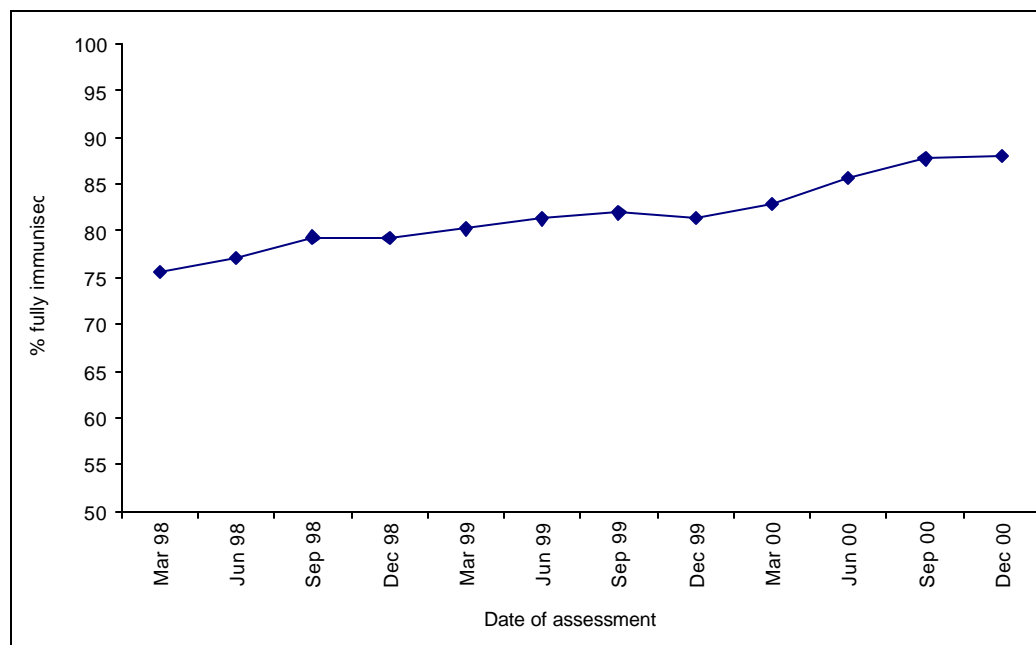
The remainder of this section examines differences in pertussis vaccine coverage in NSW by health area and age, in order to determine the most appropriate coverage figures to be used in the vaccine effectiveness estimations (Chapter 6). The proportion of the population vaccinated (PPV) is required for these calculations and is included here in the tables. PPV is calculated by dividing the proportion of fully vaccinated children by the proportion of fully vaccinated plus unvaccinated children. Partially vaccinated children are excluded from PPV calculations.

Coverage by month of age for children aged less than 2 years

A cohort of 135 825 children born between 1 March 1997 and 30 August 1998 was selected from the ACIR. Age was calculated as of 31 March 1999. The date of assessment was 30 June 1999, thus allowing a three-month grace period.

The proportion of unvaccinated children aged 6–24 months remained constant between 5–8% (*Table 4.1*). The proportion fully vaccinated increased from six to ten months of age and then remained constant between 84–87%. The proportion partially vaccinated correspondingly decreased. This most likely reflects DTP3 being given later than six months of age in some children. From 7–18 months of age the PPV

values remained quite constant. This has important implications for VE estimations. Of the infants who have received three doses of the vaccine by 12 months, 60% have received the third dose by six months, 86% by seven months and 93% by eight months. The PPV values vary even less as infants in receipt of one or two doses are excluded. The mean PPV for 7–18 month olds is 0.936 compared with 0.933 for 6–18 month olds. Taking the value at 12 months of age should be representative for infants older than seven months.

Table 4.1. Immunisation coverage by month of age for children aged 6–24 months, NSW, 1999

Month of age	% fully vaccinated[*]	% partially vaccinated[†]	% unvaccinated	PPV (full/full+none)
6	51	43	6	0.898
7	74	21	5	0.936
8	80	15	5	0.940
9	82	13	5	0.939
10	84	11	5	0.940
11	85	10	5	0.942
12	86	9	5	0.942
13	85	9	6	0.931
14	85	9	6	0.935
15	85	9	6	0.935
16	85	9	6	0.932
17	85	9	6	0.930
18	85	9	6	0.934
19	85	8	6	0.932
20	86	8	6	0.930
21	87	7	7	0.928
22	85	7	7	0.920
23	85	7	8	0.918
24	85	8	7	0.926

[*]3 doses.
[†]1 or 2 doses.

Coverage with the fourth dose increased from 32% at 18 months of age to 80% by 22 months of age (*Table 4.2*).

Table 4.2. Immunisation coverage (4 doses) by month of age for children aged 15–24 months of age, NSW, 1999

Month of age	% fully vaccinated[*]	% partially vaccinated[†]	% unvaccinated	PPV (full/full+none)
15	1	94	5	0.088
16	1	94	6	0.087
17	2	92	6	0.271
18	32	63	5	0.863
19	62	34	5	0.931
20	74	22	4	0.944
21	78	17	4	0.947
22	80	15	5	0.941
23	80	15	5	0.942
24	82	13	4	0.949

[*] 4 doses.

[†] 1-3 doses.

Coverage by health area

Health area was determined by postcode of residence. Postcodes may belong to more than one health area. This is the case with some postcodes in the Central Sydney and South Eastern Sydney health areas. As these areas had similar coverage rates and are geographically adjacent (for map see *Figure 6.1*) the two areas were combined.

12 months of age

A one-year cohort of 87 564 children born between 1 April 1997 and 31 March 1998 was selected from the ACIR and vaccination status at 12 months of age assessed as of 31 March 1999. The proportion of children recorded on the ACIR as having received all three doses of DTP ranged from 81% in the Northern Rivers health area to 90% in the New England health area (*Table 4.3*).

Table 4.3. Immunisation coverage (3 doses) by health area for children aged 12 months, NSW, 1999

Health area	% fully vaccinated*	% partially vaccinated†	% unvaccinated	PPV (full/full+none)
Metropolitan				
Central & SE Sydney	82	8	10	0.893
Northern Sydney	84	8	9	0.907
Western Sydney	83	9	7	0.920
Wentworth	87	7	6	0.939
South Western Sydney	85	9	6	0.930
Central Coast	89	8	3	0.966
Hunter	92	5	3	0.967
Illawarra	88	8	4	0.954
Total metropolitan	85	8	7	0.926
Rural				
Northern Rivers	81	10	10	0.893
Mid North Coast	84	10	6	0.936
New England	90	6	3	0.965
Macquarie	88	9	3	0.965
Mid Western	89	8	4	0.962
Far West	86	10	4	0.955
Greater Murray	89	8	4	0.959
Southern	86	9	4	0.953
Total rural	86	9	5	0.946
Total	85	8	6	0.930

*3 doses

†1-2 doses

At 2 years of age

A one-year cohort of 88 206 children born between 1 April 1996 and 31 March 1997 was selected from the ACIR and vaccination status at 2 years of age assessed as of 31 March 1999. The proportion of children recorded on the ACIR as having received all four doses of DTP ranged from 77% in the Northern Rivers health area to 89% in the Hunter health area (*Table 4.4*).

At six years of age

Children aged six years were born before the ACIR commenced so most would not have had DTP1–4 recorded as given. An estimation of coverage at six years of age was made by assuming that children recorded as having received DTP5 were fully immunised. As the proportion completely unvaccinated is not likely to be different from the cohort aged 24 months this figure was used and the percentage partially vaccinated was calculated by subtracting the sum of fully vaccinated and unvaccinated from 100. Using this method, the proportion of children aged six years who had received all five doses of DTP was estimated to range from 61% in Central and South Eastern Sydney to 79% in the Hunter health area (*Table 4.5*).

Table 4.4. Immunisation coverage by health area for children aged 24 months, NSW, 1999

Health area	4 doses (%)	3 doses (%)	1 or 2 doses (%)	No doses (%)	PPV (≥3/≥3 +0)	PPV (4 /4+0)
Metropolitan						
Central & SE Sydney	78	7	8	6	0.912	0.904
Northern Sydney	80	7	8	5	0.918	0.912
Western Sydney	80	8	7	6	0.930	0.924
Wentworth	83	8	5	5	0.952	0.948
South Western Sydney	81	8	6	5	0.941	0.935
Central Coast	85	8	3	4	0.972	0.969
Hunter	89	6	2	3	0.979	0.978
Illawarra	84	8	3	5	0.971	0.968
Total metropolitan	81	8	5	6	0.939	0.933
Rural						
Northern Rivers	77	9	8	6	0.919	0.910
Mid North Coast	81	9	5	6	0.951	0.946
New England	88	6	3	3	0.966	0.964
Macquarie	82	8	4	6	0.958	0.954
Mid Western	82	9	3	6	0.965	0.962
Far West	81	10	4	6	0.958	0.953
Greater Murray	84	8	3	5	0.968	0.966
Southern	83	8	4	5	0.962	0.959
Total rural	82	8	5	4	0.955	0.951
Total	81	8	6	5	0.942	0.937

Table 4.5. Estimated immunisation coverage (5 doses) by health area for children aged 6 years, NSW, 1999

Health Area	% fully vaccinated[*]	% partially vaccinated[†]	% unvaccinated
Metropolitan			
Central & SE Sydney	61	31	9
Northern Sydney	64	28	8
Western Sydney	66	27	7
Wentworth	70	25	5
South Western Sydney	65	29	6
Central Coast	75	22	3
Hunter	79	18	2
Illawarra	70	26	3
Total metropolitan	73	21	6
Rural			
Northern Rivers	67	25	8
Mid North Coast	75	20	5
New England	72	24	4
Macquarie	75	20	4
Mid Western	74	23	3
Far West	75	21	5
Greater Murray	77	20	3
Southern	73	22	4
Total rural	74	22	4
Total	71	24	5

[*]5 doses

[†]1-4 doses

Conclusion

Coverage with DTP vaccines among young children in Australia is currently quite high (approximately 90% for both three doses at 12 months of age and four doses at 24 months of age). As ACIR data are believed to underestimate true coverage, coverage with DTP may be even higher. Most children are vaccinated in a timely fashion, with 93% of fully vaccinated children aged 12 months receiving their third dose by eight months of age. The introduction of DTPa in Australia may have helped to improve coverage, although several other immunisation initiatives were introduced around the same time, making the evaluation of any one initiative difficult. Within New South Wales there was considerable variation in vaccine coverage between areas. This variation also existed in other States/Territories, where there were low reported coverage estimates relative to the State/Territory average in various rural areas as well as inner urban areas of most capital cities.[19]

Australia is unique in having a national immunisation register. Although the data have limitations, especially with respect to completeness, they have improved considerably since the ACIR commenced operation in 1996. The ACIR is a valuable epidemiologic tool in the study of vaccine preventable diseases — the vaccine effectiveness study presented in Chapter 6 would not have been possible without the ACIR data.

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Chapter 5

Observational methods in epidemiologic assessment of vaccine effectiveness

Introduction

Vaccine efficacy is the percentage reduction of disease incidence in a vaccinated group compared with an unvaccinated group, under ideal conditions. Vaccine efficacy studies are typically undertaken before licensure using double-blind randomised controlled trials, with all participants initially susceptible to the disease.[1] Once a vaccine has been shown to be efficacious and is licensed, the use of a placebo is unethical. Therefore an experimental design cannot be used for vaccines on the vaccination schedule, so observational methods must be employed. Furthermore, efficacy measured in clinical trials under ideal conditions may differ from effectiveness in the field under non-ideal conditions and in different populations.[2]

Vaccine effectiveness depends upon vaccine efficacy but is also affected by other factors such as transportation and storage at appropriate temperatures ('cold chain') and proper administration and timing of doses. The terms 'vaccine effectiveness' and 'vaccine efficacy' are often used interchangeably and the abbreviation VE is used for both vaccine efficacy and effectiveness.[3] In this review, VE is used as an abbreviation for vaccine effectiveness.

The Australian vaccination schedule is constantly changing as new vaccines are introduced, booster doses are added and the timing of doses is changed.[4] To maintain public and provider confidence in vaccination programs, it is essential that the effectiveness of new vaccines and changes to the schedule of existing vaccines be evaluated. The evaluation of current vaccines/schedules should also be monitored to enable detection of variations in effectiveness over time which may result from changes in the target population or in the epidemiology of the disease. In the case of new vaccines these effectiveness studies may be a component of post-licensure surveillance. In addition to post-licensure surveillance, observational vaccine effectiveness studies are particularly important when disease incidence does not predictably decrease with increased vaccine coverage, when high proportions of vaccine failure among reported cases suggest a problem with the vaccine or when issues arise that were not predicted in pre-licensure evaluations.[2]

A number of observational methodologies can be used to assess vaccine effectiveness, some of which may be incorporated into routine surveillance of vaccine preventable diseases. This paper discusses the potential biases and limitations of observational VE studies, outlines six commonly used study types and provides examples from the literature.

Calculating VE

All VE studies involve comparison of the relative risks of disease in the vaccinated group(s) with the unvaccinated group(s), hence any study type from which relative risk can be estimated can be used to calculate VE.[2] The standard equation for calculating VE as a percentage is:[2]

$$VE\,(\%) = \left(\frac{ARU - ARV}{ARU} \right) \times 100$$

where ARU is the attack rate in the unvaccinated group and ARV is the attack rate in the vaccinated group. Rearranging the formula gives the following:[2]

$$VE\,(\%) = \left[1 - \left(\frac{ARV}{ARU} \right) \right] \times 100$$

where $\dfrac{ARV}{ARU}$ is equivalent to the relative risk. In case-control studies the relative risk is approximated by the odds ratio where the disease is rare.

Protection against what? Defining the study question

Immunisation may produce more than one effect, both at the individual and the population level.[3] Individual effects include the production of an immunologic response, protection against infection or in some cases only against disease or severe disease, a reduction in the degree or duration of infectivity, or even behavioural effects such as changes in the rate of contact with potentially infectious sources.[3] Population effects include a reduction in transmission of disease and/or infection. Halloran et al[3] distinguish between indirect (the population-level effects of vaccination in unvaccinated persons), total (the population-level effects of vaccination in both vaccinated and unvaccinated persons) and the overall public health effects of the vaccination program (the weighted average of the indirect effect on unvaccinated persons and the total effect on individuals receiving the vaccination). When designing a study to estimate VE, it is important to clearly define the question of interest, in

particular whether individual and/or population effects are of interest, as this determines the appropriate choice of unit of observation, comparison group, parameter of effect, and level of information required.[3]

The question of interest is dependent upon the objective of the control program. If the objective of a control program is to reduce morbidity then high coverage with a vaccine protecting only against disease, or even severe disease, may be satisfactory.[5] In contrast, if herd immunity or eradication is the goal, the vaccine must clearly protect against infection.[5]

Potential biases in all study types

Any factor which differentially raises or lowers the apparent attack rate in either the vaccinated or unvaccinated group will bias the VE estimate. In observational VE studies there are many potential biases that need to be minimised in either the design or analysis phase of a study. In addition, the results should be presented in a way that enables the reader to judge the extent to which potential biases have operated and to estimate their impact on the estimation of VE.[2]

Case definition

Ideally, case definitions should be sensitive and specific. Whilst a high sensitivity gives a more precise estimate of VE, the point estimate is not unduly affected by a low sensitivity as long as the case definition has equal sensitivity in the vaccinated and unvaccinated groups.[2] This is a problem with pertussis, as vaccinated persons often experience a milder form of the disease which is less likely to fit a clinical case definition. In these situations, it is the effectiveness of the vaccine against more serious disease, rather than against all disease or infection, that is being estimated.

For VE estimation the specificity of a case definition is generally more crucial than its sensitivity, as the misclassification of other illness as cases would equalise the attack rates in the two groups resulting in a falsely low VE estimate.[2] The rarer the disease, and the greater the incidence of misclassified illness, the greater the bias toward low VE.[2] This bias is even greater when the case definition has low sensitivity.[2]

Point estimates of pertussis VE increase with increasing specificity of clinical case definitions[2] or when based on clinically severe or bacteriologically positive cases.[5] The same phenomenon has been observed in pertussis vaccine trials, where the greater the clinical severity of cases accepted as pertussis, the higher the VE estimates.[6] However, although laboratory confirmation increases specificity, it may lead to other biases as a result of problems with case ascertainment.[2]

Case ascertainment

In a pre-licensure trial, bias in case ascertainment is minimised by randomisation and by blinding the observer to vaccination status, neither of which is generally possible in an observational study. In observational studies, vaccinated and unvaccinated persons are self-selected groups who may not have equal access to health care services, hence equal case detection cannot be assured.[2]

Studies using passively notified cases are particularly prone to bias in case ascertainment, as individuals with disease may not all have an equal probability of being notified. If notifications correlate with good public health practice and easy access to medical services, and hence are associated with high vaccine uptake, then vaccinated individuals may be preferentially notified, resulting in an underestimate of VE.[5] Or if, as is the case with pertussis,[6,7] the vaccine gives greater protection against more severe disease and there is a correlation between clinical severity and the probability of a physician recognising and then notifying a case, VE will be overestimated.[5] A more serious problem occurs if, independently of disease severity, unvaccinated cases are more (or less) likely to be recognised and/or notified than vaccinated cases. For example, a physician's knowledge that a child is fully vaccinated against pertussis could reduce the index of suspicion that an illness is in fact pertussis, resulting in an overestimate of VE.[5] The extent of this bias is difficult to estimate.

A pertussis outbreak investigation in the United Kingdom in 1987 found that only 31 of 90 children with bouts of coughing lasting for two or more weeks followed by whooping, vomiting or choking/turning blue (probable cases) were notified.[8] Using notified cases only the VE estimate was 88%. This fell to 75% when probable cases were included and 68% when the case definition included all children with bouts of

coughing lasting at least two weeks.[8] The author found that notified children were younger and less likely to be vaccinated, suggesting that children were less likely to be diagnosed and notified as pertussis if they were known to have been vaccinated.

Ascertainment of vaccination status

Classification errors in vaccination status reduce VE estimates unless there is a bias towards misrepresenting vaccinated cases as unvaccinated.[5] Studies relying on parental recall of a child's vaccination status tend to overestimate vaccination coverage, whereas studies which require verification with written records may underestimate vaccination coverage.[9]

VE estimation for diseases against which more than one dose of vaccine is necessary for full protection require information on the number of doses of vaccine given. If partial vaccination affords some protection against disease, then the way partially vaccinated cases are handled in the analysis can affect the VE estimate. If partially vaccinated cases are classified as unvaccinated but still receive some protection, the attack rate in the unvaccinated is lowered, whereas classifying partially vaccinated cases as fully vaccinated will raise the attack rate in the vaccinated. If the effectiveness of the full course of vaccination is being measured, then cases who are partially vaccinated should be excluded from the analysis wherever possible.[2]

Comparability of vaccinated and unvaccinated groups — potential confounding

In randomised controlled trials potentially confounding variables are randomly distributed among the experimental and control groups. In observational studies the groups may differ in many ways, only some of which may be recognised by the investigator.[2] Unrecognised or unmeasurable differences between the experimental and control groups, such as increased susceptibility due to poor nutrition in unvaccinated marginalised groups, may pose serious threats to validity. However, the most important potential confounder in VE studies is exposure to disease. VE calculations generally assume equal exposure to infection in vaccinated and unvaccinated individuals or groups. Exposure to infection may in turn be associated with variables such as age and place of residence.

For a variable to be considered as a confounder it must be independently related to both the risk of disease and vaccination status. Not all variables which differ in frequency between vaccinated and unvaccinated groups fulfil this requirement. Orenstein et al[2] give the example of a case-control study whereby cases, by definition, will have been more exposed to disease than controls but this difference in exposure does not bias the VE estimate unless the probability of exposure is also related to the probability of being vaccinated. If groups who have a greater risk of exposure (eg, children who attend day care) are more likely to be vaccinated, then VE will be underestimated.

The indirect effects of vaccination can affect the probability of exposure in both vaccinated and unvaccinated groups, but not necessarily to an equal extent. If VE is estimated at a population level, where the study group comprises exposed and unexposed individuals, then whether or not the vaccine has been administered randomly will have a significant effect on the estimate.[10] If groups with high vaccine coverage are at low risk of exposure to infection, for example because of herd immunity, and VE is viewed as the degree of protection afforded to an individual who has been exposed to the disease, then clustering of vaccine status in the population may produce falsely high VE estimates.[5,10] Similarly, groups with low vaccine coverage may have greater exposure to infection resulting in falsely low VE estimates.[2] However, if the overall effectiveness of the vaccination program is being studied, then it is appropriate to include the indirect protection of vaccination in the calculation.

Age

Age may be associated with both the probability of vaccination and the probability of having had prior exposure to the disease. Where immunity from disease and/or vaccination is acquired at a young age and diminishes with time, age may be a proxy measure for time since vaccination. Data should be analysed separately for narrow age groups or otherwise standardised for age.[5]

Prior disease

If prior disease is not associated with vaccination status then VE estimates will be unbiased.[2] However, vaccinated and unvaccinated groups may differ with respect to

prior disease, in which case ignoring previous histories may bias the VE estimate.[2] However, the effect of this bias must be weighed against the problem of obtaining valid histories, which for some diseases may not be feasible.

Observational study types

A variety of observational methods may be used to estimate VE including the well established cohort and case-control design. In addition, household contact studies, the screening method, case cohort studies and coverage surveys are commonly used. Each methodology has its advantages and disadvantages and methodological problems have been identified for all study types. In order to identify observational studies evaluating VE in Australia and New Zealand, the Medline database from May 1987 to May 2000 was searched for the textwords 'vaccine efficacy' or 'vaccine effectiveness' and 'Australia' or 'New Zealand'. Only ten studies were identified (*Table 5.1*).

Table 5.1. Observational studies evaluating VE in Australia and New Zealand

Authors	Study type	Disease	Setting
Herceg A.[11]	Cohort	Pertussis	ACT school
Gidding HF, Hills S, Selvey L, Roberts LA, Johnston S. [12]	Cohort	Measles	Rural Queensland town
Jeremijenko AM, Kelly H, Patel M.[13]	Cohort	Measles	Western Australian town
Patel MS, Lush D.[14]	Cohort	Measles	Central Australia
Cheah D, Lane JM, Passaris, I.[15]	Cohort	Measles	Canberra
McDonnell LF, Jorm L, Patel MS.[16]	Matched case-control	Measles	Western Sydney
Bower C, Condon R, Payne J, Burton P, Watson C, Wild B.[17]	Case-control	*Haemophilus influenzae* type b	Western Australia
Herceg A.[18]	Screening	*Haemophilus influenzae* type b	Australia
Blakely T, Mansoor O, Baker M.[19]	Screening	Pertussis	New Zealand
Harrison GP, Durham, GA. [20]	Screening*	Measles	New Zealand

*Described by the authors as 'outbreak investigation using attack rates' but the methodology most closely resembles the screening method.

Cohort studies

A cohort design is most appropriate when a discrete population at risk can be defined.[21] Most cohort studies of VE have been retrospective and have generally been undertaken as part of an outbreak investigation. The cohort, often based in a school, childcare centre or geographically defined area, is defined and the vaccination status of all members of the cohort is ascertained. The relative risk of disease in the vaccinated compared with the unvaccinated group is then calculated thus enabling the calculation of VE. Examples of disease outbreaks in Australia where VE has been measured using a cohort study design include a pertussis outbreak in an Australian Capital Territory school[11] and measles outbreaks in Bunbury, Western Australia,[13] Canberra,[15] Central Australia[14] and rural Queensland.[12]

Orenstein et al[1] list five criteria which minimise bias in cohort studies which are part of an outbreak investigation:

1) absence of substantial prior disease activity in the studied age group

2) both vaccinated and unvaccinated individuals are included in the study population

3) adequate numbers in the population in the age group to be studied

4) high overall attack rate and

5) good vaccination records available.

Retrospective cohort studies have also been used to estimate pertussis VE in non-outbreak situations. An example is in child-care centres and schools in Quebec, Canada.[22]

The classification of study types is not always as simple as it may first appear. One study in the literature identified vaccinated and unvaccinated cases by an enhanced notification system and used the results of a previous coverage survey to construct a theoretical cohort of vaccinated and unvaccinated children of a specific age group.[23] Although the authors called this a retrospective cohort study, the design did not fulfil the criteria for a cohort study, in that subjects were not selected on the basis of exposure (vaccination) but on the outcome of interest (being notified as having pertussis). Cases were then compared with population controls. The theoretical cohort of unvaccinated children was not followed up to ascertain whether the children developed pertussis. More appropriate study designs would have been either the screening method or the case-cohort method. However, the cohort and screening methodologies yield very similar VE estimates: 76% using the cohort method[23] and 74% using the screening method. This is not surprising, as the screening method VE equation is derived from the cohort method. A New Zealand study of measles notifications used similar methodology, referring to the study design as 'outbreak investigations using attack rates.'[20]

Household contact studies

Household contact studies are used to measure the secondary attack rate of disease in household contacts of index cases. VE is calculated by combining the total population of the households under study, excluding the primary and co-primary cases, to form

vaccinated and unvaccinated cohorts.[2] The methodology corrects for potential differences in exposure between vaccinees and non-vaccinees, thus reducing the bias that may result from differential exposure.[1] Orenstein et al[1] comment that next to outbreak investigations, this technique has been evaluated most and is an acceptable alternative to outbreak investigations. However, Fine and Clarkson[5] point out that the relative simplicity of the household secondary attack method should not be taken as license for its uncritical application and interpretation. No Australian or New Zealand household contact studies were identified in the literature.

Pertussis VE estimates derived from household secondary attack rates are generally lower than those obtained by other methods, regardless of diagnostic criteria used for case ascertainment.[24] One possible bias in these study types, which relates to pertussis vaccines and level of exposure, is the assumption that these vaccines are less effective under conditions of heavy exposure such as those within households.[5] The study of family contacts of ascertained cases, which are highly selected populations, may introduce bias. If vaccine uptake is non-random, then most or all of the vaccinated individuals in the study will be included because of a prior vaccine failure in the household (ie, the index case). Possible risk factors for vaccine failure are likely to be shared by members of the household, thus introducing a bias against the vaccine.

Again assuming non-random vaccine uptake and the likelihood that household contacts share the same vaccination status of the primary case, studies of situations in which pertussis is introduced to a household by a vaccinated case may be biased in favour of the vaccine.[5] This arises from the reduced severity of disease in vaccinated persons which may result in close contacts being exposed to fewer bacilli than the contacts of unvaccinated individuals, thus reducing the risk of infection preferentially among vaccinated contacts and raising VE estimates.

Households with larger rather than smaller numbers of cases are more likely to be identified and included in a study.[5] This ascertainment bias is likely to lower vaccine effectiveness as households in which the vaccine is working best would be selectively excluded from the study.[5]

Secondary attack rates in clusters

This is a modified form of household contact studies that has been used in urban and semi-urban settings.[1] This method is less rigorous than household contact studies due to the more questionable comparability of exposure of vaccinees and non-vaccinees, but is logistically easier to carry out than a household contact study.[1] Orenstein et al[1] suggest that further evaluation of this method is needed.

Case-control studies

In a case-control study, cases are selected on the basis of having the disease of interest, and controls on the basis of being comparable to cases but without having the disease, so that the odds ratio of vaccination can be calculated. The traditional VE equation cannot be used in case-control studies[1] as cases represent one sampling fraction of all cases and the controls represent a different sampling fraction of the population that is not ill.[25] As the sampling fraction is unknown, the total populations of vaccinated and unvaccinated people cannot be calculated and therefore neither can attack rates.[1] However, for rare diseases, the odds ratio approximates relative risk and so can be used to estimate VE. Although the VE estimate will be erroneously high when the attack rate in vaccinated persons is greater than 10%,[1] this is usually not the case and therefore the error will not be of an important magnitude.[1] In Australia case-control studies have been used to estimate VE for measles in Western Sydney[16] and for *Haemophilus influenzae* type b infection in Aboriginal children in Western Australia.[17]

Screening method

Using the screening method, VE is estimated by comparing the proportion of cases who are vaccinated (PCV) with the proportion of a comparable group in the population who are vaccinated (PPV). The screening method equation is:[26]

$$VE = 1 - \left[\left(\frac{PCV}{1 - PCV} \right) \left(\frac{1 - PPV}{PPV} \right) \right]$$

Figure 5.1 shows the curves generated from this equation. As can be seen from *Figure 5.1*, an overestimate in PPV will result in an overestimate of VE. The error is particularly marked when vaccine coverage is greater than 80%.[1]

Figure 5.1. Relationship between the proportion of cases vaccinated (PCV) and the proportion of population vaccinated (PPV) for eight values of vaccine effectiveness (VE)
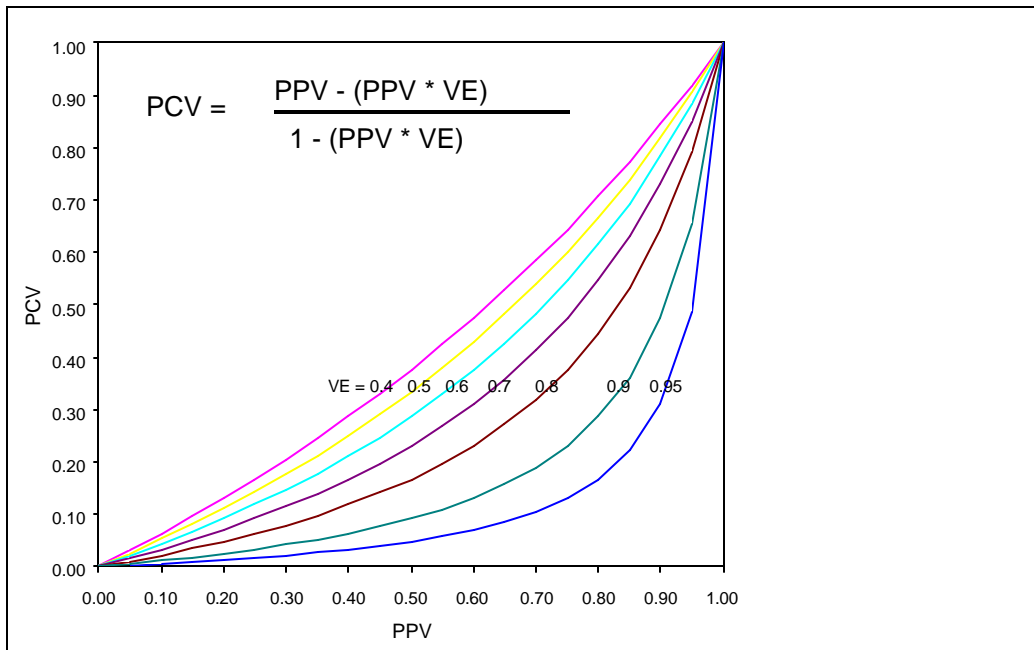
Source: Orenstein et al.[1]

The screening method is a relatively rapid way of estimating VE which has been used to estimate pertussis VE in the Netherlands,[27] the United States,[28] Nova Scotia,[29] the United Kingdom[30] and New Zealand.[19] In Australia it has been used to estimate the VE of *Haemophilus influenzae* type b[18] but has not previously been used to estimate the VE of pertussis. The screening method is particularly useful for routine monitoring of VE or in circumstances where data on the vaccination status of cases only are available. Provided that any biases remain reasonably constant, the screening method may be used for monitoring changes in VE over time. It should not be relied upon for precise VE estimates.[1] An overestimate in PPV will result in an overestimate of VE and this error is particularly noticeable when vaccine coverage is greater than 80%.[1]

Care must be taken to stratify the data by possible confounding variables such as age and location. If different population groups have different coverage figures then the groups should be analysed individually. Farrington[26] illustrates the effect of pooling

population coverage figures in an example of two cohorts, A and B, of equal size. In cohort A there are 100 cases, 50 of whom are vaccinated and the PPV is 0.9. In cohort B there are 10 cases, one of whom is vaccinated and PPV is 0.5. The screening method VE estimate is 89% in each cohort. However, if the cohorts are combined, then there are 110 cases, 51 of whom are vaccinated, while the combined value of PPV is 0.7 which produces a VE estimate of only 63%.[26]

Case-cohort

This study type is also known as case-base and is similar to the screening method except that vaccination status is sampled in population controls rather than using an assumed true value of PPV.[26]

Coverage surveys

Where disease is common, a cross-sectional survey may be undertaken in a geographically defined area.[2] This approach is conceptually similar to an outbreak investigation in which study subjects are categorised retrospectively according to their vaccination status. The relative risk of disease in the unvaccinated group compared with the risk in the vaccinated group can be calculated (except that the risk period in a coverage survey is generally longer than in an outbreak investigation).[2] Study participants must be old enough to have lived through a sufficient period of risk of disease and those who receive vaccination after the period of observation begins should be excluded from the analysis, leaving a cohort of vaccinated and unvaccinated members.[2] Persons whose vaccination status or disease history is uncertain must also be excluded from the analysis.[1] There has been only limited use of this approach and modifications may be required as experience with the technique accumulates.[1]

Conclusion

There are a variety of observational methods which can be used to estimate VE, none of which is perfect. The screening method is the cheapest and most rapid means of determining whether there is a major problem with the vaccine, as all that is required is a reliable estimate of the proportion of cases who are vaccinated and an estimate of the vaccine coverage in the population at risk.[1] The great advantage of this method is that it allows for ongoing monitoring of VE where these data are available. If the screening method results suggest that VE is lower than expected, this should be

confirmed by more rigorous methods. Of the more accurate observational methods available, cohort studies undertaken during an outbreak investigation offer the simplest means of VE estimation and are the preferred study design where the situation permits.[1] The most appropriate study design will depend upon the specifics of the particular situation such as availability of resources, access to records, the number and distribution of cases and the availability of population coverage data.

Whilst results obtained using observational methods may be distorted due to unavoidable bias, it may still be possible to calculate a sufficiently good estimate of VE for operational purposes.[31] Potential biases should be considered in the design phase of a VE study and steps taken to minimise them if possible. All reports of VE studies should include a discussion of the biases which may have been operating and their possible effects on VE estimates. Provided that these steps are taken, observational methods provide valuable tools for the evaluation of vaccination programs. To date, few observational VE studies have been undertaken in Australia and New Zealand, suggesting the under-utilisation of these methods.

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Chapter 6

Effectiveness of pertussis vaccination in New South Wales children

Part A: Effectiveness of pertussis vaccination in NSW children, 1993 to 1998

Introduction

As demonstrated in Chapters 2 and 3, notification data can provide much useful information about the epidemiology of pertussis. In addition to the analysis and interpretation of disease surveillance and vaccination coverage data, there is a need for a system capable of detecting major shifts in the effectiveness of the pertussis vaccination program. Further indications for monitoring pertussis vaccine effectiveness (VE) in Australia include evidence of a major change in VE elsewhere,[1] a lack of effectiveness data on the whole-cell vaccine used in Australia and the recent introduction of acellular vaccines.

This chapter combines New South Wales (NSW) notification data (Chapter 3) with vaccine coverage data from the ACIR (Chapter 4). It aims to estimate the effectiveness of the primary course (doses 1-3 due at 2, 4 & 6 months of age) of the pertussis vaccination program in NSW children using the screening method. The screening method compares the proportion of cases who are vaccinated (PCV) with the proportion of a comparable group in the population who are vaccinated (PPV). It is a relatively inexpensive and rapid method which has been used to estimate pertussis VE in Nova Scotia,[2] the United Kingdom,[3] the United States,[4] New Zealand[5] and the Netherlands.[1] In Australia it has been used to estimate the VE of *Haemophilus influenzae* type b[6] but not pertussis vaccines. This study also aims to evaluate the usefulness of applying the screening method to surveillance data, using coverage data from the Australian Childhood Immunisation Register (ACIR), and to consider the application of this method for future VE estimations.

Methods

Study Subjects

All notified cases of pertussis aged eight months to 14 years with disease onset dates between January 1993 and December 1998 were selected from the Notifiable Diseases Database (NDD) using the Health Outcomes and Information Statistical Toolkit (HOIST),

NSW Department of Health. Cases aged less than eight months were excluded, to allow time for infants to complete the primary vaccination schedule for pertussis.

The NDD includes information on whether a case was vaccinated (yes/no/unknown/missing) and how many doses of vaccine the case had received. Vaccination status was calculated based on the number of doses of pertussis vaccine recorded and the child's age. The NDD does not contain information on date of vaccination nor on the type of vaccine administered (whole-cell or acellular). Except where stated otherwise, fully vaccinated means having received at least 3 doses of a pertussis-containing vaccine. Incompletely vaccinated children were excluded from VE analyses, which were comparisons of fully vaccinated with unvaccinated groups, the approach recommended by Orenstein.[7]

NSW is divided into 17 area health services, eight of which are rural (*Figure 6.1*). Health areas in which vaccination status was unknown for more than 25% of cases were excluded. Residents of New England Area Health Service were excluded due to small numbers. As Southern Area Health Service had very small numbers of cases and is geographically adjacent to Greater Murray Area Health Service, these two areas were combined, as were Central Sydney and South Eastern Sydney. The areas studied include four metropolitan areas (Central Sydney, South Eastern Sydney, Western Sydney and Wentworth) and three rural areas (Southern, Greater Murray and Northern Rivers). These areas comprise 46% of the NSW population.

Figure 6.1. Health Areas of NSW
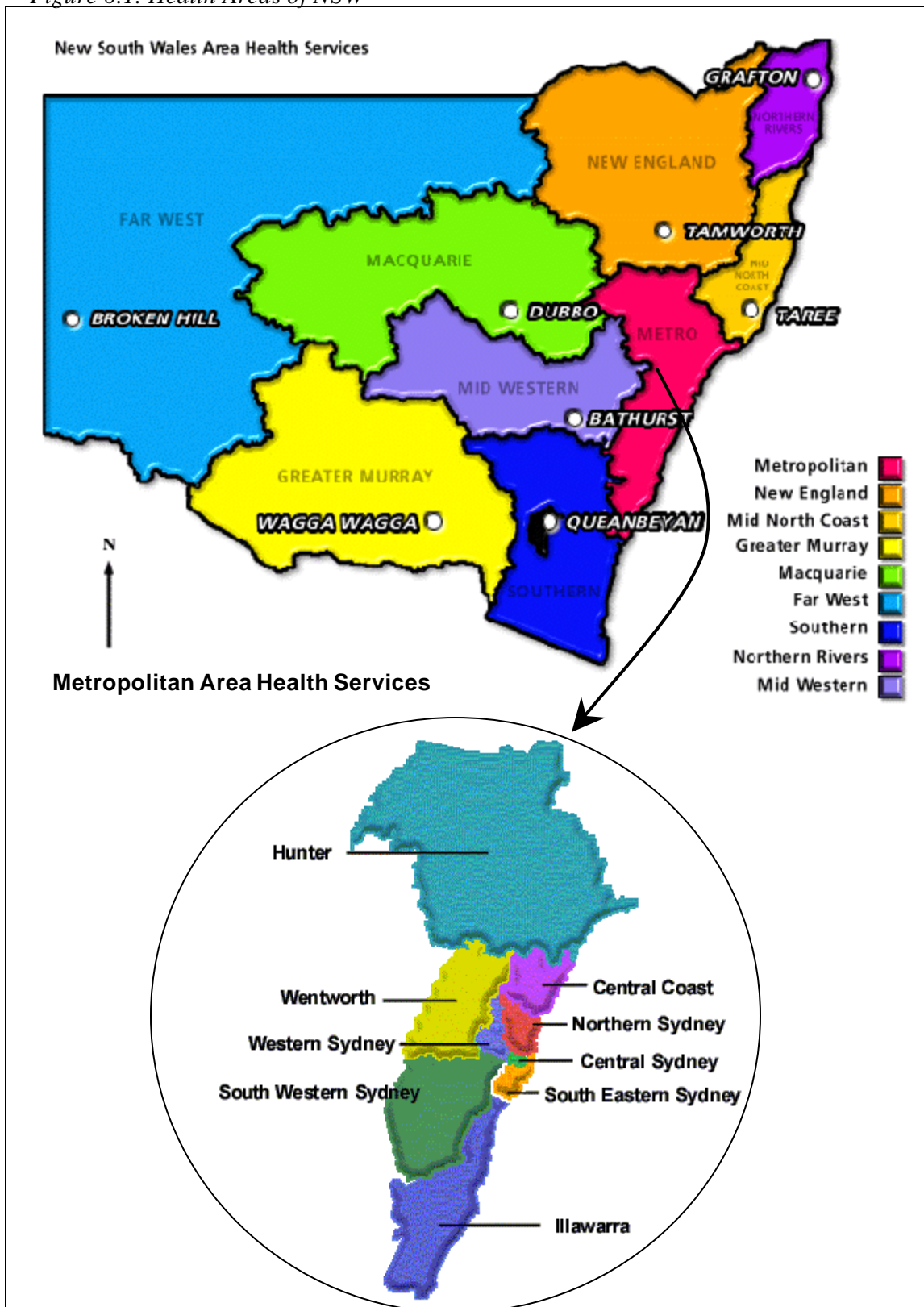
Source: NSW Health Website — www.health.nsw.gov.au/iasd/areas/

Population estimates

Population coverage estimates were taken from the Australian Childhood Immunisation Register (ACIR). The ACIR contains information on the vaccination status of children born since 1 January 1996, who are either registered with Medicare or have had a vaccination encounter reported to the ACIR. A 12-month cohort of 87 564 children born between 01/04/97 and 31/03/98 was selected from the ACIR. Vaccination status at 12 months of age, using the third-dose assumption, was assessed as of 31/03/99. The third-dose assumption classifies a child as fully vaccinated as long as the third dose is recorded, irrespective of recording of the previous two doses.[8] Health area was determined by postcode of residence. Incompletely vaccinated children were excluded and the proportion of the population vaccinated (PPV) for each area was calculated by dividing the number of children fully vaccinated by the sum of the number of children fully vaccinated and unvaccinated. It was assumed that PPV did not change over the study time period. The effect of using a pooled PPV value (ie, not stratified by health area) was examined. In addition, a sensitivity analysis was undertaken where it was assumed that two thirds of children recorded on the ACIR as having received one or two doses of vaccine had in fact received three, and one-third of the children recorded as having received no doses of vaccine had in fact received all three doses.

VE estimation

VE was estimated by fitting a logistic regression model using the method described by Farrington, whereby the number of vaccinated cases is regarded as from a binomial distribution with PCV as the parameter and number of cases (N) as the index.[9] Proc Genmod in the software package SAS[10] was used for modelling. Logit PPV was specified as an offset in the model, and the variables age group, health area of residence and year of disease onset were included as potential confounders, giving the equation:

$$\text{logit (PCV)} = \text{logit (PPV)} + a + b_1x_1 + b_2x_2 + b_3x_3$$

where PCV = the proportion of cases vaccinated, x_{1-3} are the potentially confounding variables and b_{1-3} are the parameter estimates of those variables.

The base model containing the three potentially confounding variables was fitted and the significance of each one was tested (using the type3 option in SAS). The effects of all 2-way interactions were tested for statistical significance ($p<0.05$) by adding them in turn to the base model. VE was calculated for each combination of age group, area and year by

subtracting the exponentiation of the estimated linear predictor (XBETA in SAS) from one. Confidence intervals were calculated in a similar way using the standard error of the linear predictor (STD in SAS).

The effect of including year of age as an explanatory variable was examined and the decision to include four age groups (8-23 months, 2-4 years, 5-8 years and 9-13 years) was based on these results. The first three age groups correspond with eligibility to receive three, four and five doses of a pertussis-containing vaccine respectively.

In order to obtain overall estimates by area and age group, the average of the relevant parameter estimates for year, including the interaction terms, was calculated. To obtain overall estimates by year and age group, the parameter estimates for area, including the interaction terms, were weighted by population. The adjusted estimates of year and area were used to calculate VE for each age group, adjusted for year and area. The variances of these adjusted parameter estimates were calculated from the covariance matrix using Excel.[11] Confidence intervals were calculated using these estimates.

Variations on the model

The effects of the following were examined:

- Grouping years with a high number of notifications (the 'epidemic years' 1993 and 1997) and years with a lower number of notifications ('non-epidemic years')

- Grouping metropolitan health areas together and rural health areas together

- Using only one value for PPV (ie, not one for each health area)

- Increasing PPV — assuming that two-thirds of children recorded as having received one or two doses of vaccine had in fact received three, and one-third of the children recorded as having received no doses had received all three doses

- Requiring cases aged over 18 months to have received four doses of a pertussis containing vaccine in order to be classified as fully vaccinated (ie, classifying cases aged over 18 months who had only received three doses as partially vaccinated and excluding them from analyses)

- Classifying partially vaccinated children as unvaccinated

- Including only cases who were laboratory confirmed (by culture or serology).

Results

Pertussis cases

In NSW from 1993 to 1998, 5447 cases of pertussis in children aged 8 months to 13 years from a known health area were notified. Of these, 2795 cases (51%) were resident in areas eligible for inclusion in VE analyses. There was considerable variation among health areas, in both notification rate and the vaccination status of cases (*Table 6.1*). After excluding the 348 cases whose vaccination status was unknown and the 121 cases who had received only one or two doses of the vaccine, there were 2326 cases eligible for the VE analyses.

Vaccination status of notified cases

Of the 2326 cases eligible for inclusion in the study, 1227 (53%) had received at least three doses of a pertussis-containing vaccine. Most (90%) of the vaccinated cases aged two years or older had received a fourth dose, while 29% of vaccinated 5–8 year olds and 15% of vaccinated 9–13 year olds had also received a fifth dose of vaccine.

Table 6.1. Number of notifications and average annual notification rates by health area and vaccination status in children aged 8 months to 13 years, NSW, 1993–1998

Area	full	%	partial	%	none	%	unk*	%	Total	Rate[†]
Central Sydney	63	28	5	2	109	49	45	20	222	54
Western Sydney	307	54	22	4	148	26	94	16	571	74
Wentworth	291	64	19	4	106	23	38	8	454	111
Sth Eastern Sydney	244	47	23	4	158	31	93	18	518	80
Northern Rivers	124	19	24	4	450	70	47	7	645	218
Greater Murray	165	60	22	8	70	26	16	6	273	84
Southern	33	29	6	5	58	52	15	13	112	52
Total	1227	44	121	4	1099	39	348	12	2795	91

*unk=unknown

[†]Average annual notification rate per 100 000 population aged 8 months to 13 years.

Vaccination status variations

The oldest age group had the highest proportion of both vaccinated cases and cases whose vaccination status was unknown (*Table 6.2*).

Table 6.2. Vaccination status of notified cases and average annual notification rates by age group, NSW, 1993–1998

Age group	Fully vaccinated* n (%)	Partially vaccinated[†] n (%)	Un-vaccinated n (%)	Unknown n (%)	Total n	PCV (%)	Rate[‡]
8-23 mth	62 (31)	16 (8)	103 (51)	20 (10)	201	37.6	64
2-4 yrs	191 (45)	16 (4)	179 (42)	38 (9)	424	51.6	60
5–8 yrs	408 (41)	51 (5)	441 (44)	105 (10)	1,005	48.1	109
9-13 yrs	566 (49)	38 (3)	376 (32)	185 (16)	1,165	60.1	102
Total	1,227 (44)	121 (4)	1,099 (39)	348 (12)	2,795	52.8	91

[*]3 doses

[†]1-2 doses

[‡]Average annual notification rate per 100 000 population.

The vaccination status of children in areas where at least 75% of notifications had a known vaccination status was compared with that in the other areas. In health areas where at least 75% of notifications had a known vaccination status, PCV was 0.583 compared with only 0.280 in areas where less than 75% of notifications had a known vaccination status. This difference was statistically significant ($\chi^2_1 = 152$, p<0.001).

Population estimates

Northern Rivers had the lowest proportion of fully vaccinated children and Southern/Greater Murray had the highest (*Table 6.3*). The population values used in the sensitivity analysis are shown in *Table 6.4*.

Table 6.3. Vaccination coverage by health area for children aged 12 months, NSW, 1993–1998

Health area	% fully vaccinated*	% partially vaccinated[†]	% unvaccinated[‡]	PPV (full/full+none)
Central & SE Sydney	82	8	10	0.893
Western Sydney	83	9	7	0.920
Wentworth	87	7	6	0.939
Northern Rivers	81	10	10	0.893
Southern & Greater Murray	88	8	4	0.957
Total	85	8	6	0.930

[*]3 doses, [†]1-2 doses, [‡]0 doses.

Table 6.4. Increased vaccination coverage used in sensitivity analysis by health area for children aged 12 months, NSW, 1993-1998

Health area	% fully vaccinated[*]	% partially vaccinated[†]	% unvaccinated[‡]	PPV (full/full+none)
Central & SE Sydney	91	3	7	0.933
Western Sydney	92	3	5	0.950
Wentworth	94	2	4	0.961
Northern Rivers	90	3	6	0.933
Southern & Greater Murray	95	3	3	0.973
Total	92	3	5	0.950

*3 doses, [†]1-2 doses, [‡]0 doses.

Year of age

In order to determine the effect of age on VE, a model was fitted using year of age as the only explanatory variable. This model had a poor fit (deviance = 814 with 372 degrees of freedom). The parameter estimates for 2–4 and 6–12 year old children were not significantly different from 13 year olds (the reference group). VE was highest in infants aged less than 12 months and lowest in 9 year olds (*Figure 6.2*). The decrease in VE with increasing age was not linear, hence including age as a continuous variable in the model would have been inappropriate, and in further analyses four age groups were used.

Figure 6.2. Estimated VE for each year of age, with age as the only explanatory variable, 1993 – 1998
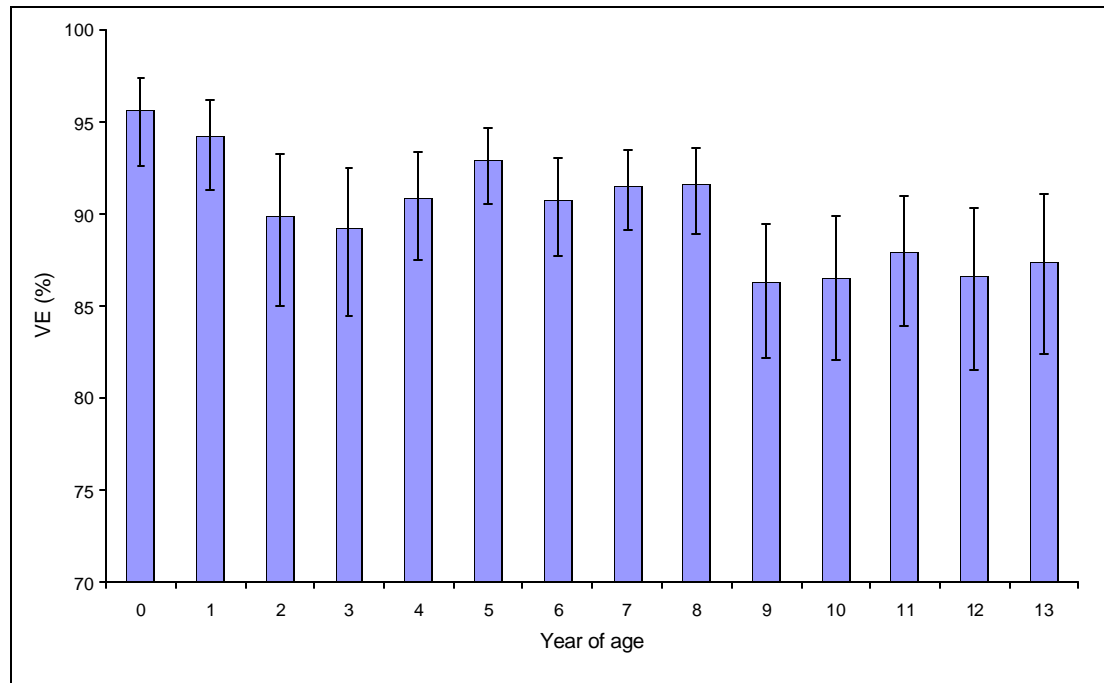
Fitting the model

The model with no explanatory variables was a poor fit (deviance=538 with 119 df). VE, calculated from this base model, was 90.1% (95% CI 88.2 to 91.7%). The addition of each explanatory variable by itself significantly improved the fit of the model (*Table 6.5*). Health area was the most significant explanatory variable. All variables remained significant in the model in which all three were included (p<0.0001). Excluding cases which were not laboratory confirmed improved the fit of the model even further.

Table 6.5. Summary of models, 1993–1998

Explanatory variable(s)	Dev*/ df[†]	χ^2	df	p-value
None	4.52			
Age	4.30	40	3	<0.0001
Year	3.88	96	5	<0.0001
Area	2.67	232	4	<0.0001
Age + year + area	1.98			
Age + year + area + year*area	1.32			
Age + year + area + year*area (for lab confirmed cases only)	1.19			

*Dev=deviance
[†]df=degrees of freedom.

The final model included age group, year of onset and area (the base model), plus the interaction between area and year. This model had a deviance of 114 on 87 degrees of freedom, suggesting that the model was slightly over-dispersed (p=0.03). When the model was re-scaled by dividing the deviance by the degrees of freedom to incorporate the extra variability, as recommended by Farrington,[9] the width of the 95% confidence intervals of the VE estimates increased. In the final model all variables were significant (p<0.001).

VE Estimates

VE estimates from the final model for each of the four age groups, stratified by health area and year, were calculated (*Tables 6.6 to 6.9*).

Table 6.6. Number of vaccinated cases (CV), total number of cases (n) and VE estimates for children aged 8–23 months by NSW health area, 1993–1998

Health area	year	CV	n	VE (%)	95% CI (%)
Central & SE Sydney	1993	1	3	88.6	79.4 to 93.7
	1994	6	6	85.8	71.2 to 93.0
	1995	2	3	89.9	73.0 to 96.2
	1996	1	4	93.8	86.4 to 97.2
	1997	4	13	94.9	91.7 to 96.8
	1998	0	3	93.3	83.9 to 97.2
Northern Rivers	1993	0	6	97.7	94.6 to 99.0
	1994	3	16	98.5	97.4 to 99.2
	1995	1	10	98.2	96.7 to 99.0
	1996	1	2	97.7	93.0 to 99.3
	1997	3	11	98.3	96.8 to 99.1
	1998	2	2	92.2	70.9 to 97.9
Western Sydney	1993	2	3	94.9	89.2 to 97.6
	1994	4	8	90.4	80.7 to 95.2
	1995	1	2	83.0	60.8 to 92.6
	1996	1	6	92.9	85.5 to 96.5
	1997	8	12	89.6	82.3 to 93.8
	1998	4	6	83.4	58.3 to 93.4
Wentworth	1993	0	4	97.0	93.4 to 98.7
	1994	0	1	96.9	92.9 to 98.6
	1995	1	4	90.9	80.6 to 95.7
	1996	2	4	84.8	50.6 to 95.3
	1997	7	10	87.0	76.4 to 92.8
	1998	0	1	76.1	41.4 to 90.3
Southern & Greater Murray	1993	1	3	99.4	92.5 to 99.9
	1994	1	2	99.2	97.5 to 99.7
	1995	0	6	97.4	95.1 to 98.7
	1996	0	3	99.1	97.7 to 99.6
	1997	4	8	96.8	93.8 to 98.4
	1998	2	3	80.1	55.9 to 91.0

Table 6.7. Number of vaccinated cases (CV), total number of cases (n) and VE estimates for children aged 2–4 years by NSW health area, 1993–1998

Health area	year	CV	n	VE (%)	95% CI (%)
Central & SE Sydney	1993	10	19	77.8	63.6 to 86.4
	1994	9	14	72.4	47.3 to 85.5
	1995	4	5	80.3	49.4 to 92.4
	1996	1	2	87.9	74.6 to 94.3
	1997	21	47	90.0	85.6 to 93.0
	1998	2	4	87.0	70.1 to 94.3
Northern Rivers	1993	2	7	95.5	90.1 to 98.0
	1994	12	39	97.1	95.4 to 98.2
	1995	7	26	96.4	94.1 to 97.8
	1996	3	9	95.6	87.1 to 98.5
	1997	5	19	96.8	94.3 to 98.2
	1998	2	4	84.7	45.1 to 95.8
Western Sydney	1993	3	9	90.1	80.4 to 95.0
	1994	5	9	81.3	64.2 to 90.2
	1995	8	8	66.8	27.9 to 84.7
	1996	8	14	86.1	73.4 to 92.8
	1997	20	32	79.6	68.7 to 86.7
	1998	5	6	67.7	20.7 to 86.8
Wentworth	1993	4	8	94.2	87.9 to 97.2
	1994	5	11	93.9	87.1 to 97.1
	1995	11	15	82.2	64.8 to 91.0
	1996	1	2	70.2	5.0 to 90.7
	1997	10	15	74.5	57.0 to 84.9
	1998	12	13	53.4	-7.3 to 79.8
Southern & Greater Murray	1993	0	1	98.8	85.4 to 99.9
	1994	1	3	98.4	95.3 to 99.5
	1995	4	4	95.0	91.0 to 97.2
	1996	1	5	98.2	95.7 to 99.2
	1997	7	11	93.8	88.5 to 96.7
	1998	8	9	61.2	18.9 to 81.4

Table 6.8. Number of vaccinated cases (CV), total number of cases (n) and VE estimates for children aged 5–8 years by NSW health area, 1993–1998

Health area	year	CV	n	VE (%)	95% CI (%)
Central & SE Sydney	1993	34	47	81.4	70.8 to 88.1
	1994	20	31	76.8	57.2 to 87.5
	1995	4	5	83.5	58.1 to 93.5
	1996	8	18	89.9	79.6 to 95.0
	1997	37	86	91.6	88.5 to 93.8
	1998	6	10	89.1	75.6 to 95.1
Northern Rivers	1993	5	15	96.3	91.9 to 98.3
	1994	15	90	97.6	96.3 to 98.4
	1995	11	67	97.0	95.3 to 98.1
	1996	2	10	96.3	89.2 to 98.7
	1997	7	56	97.3	95.4 to 98.4
	1998	1	3	87.2	54.2 to 96.4
Western Sydney	1993	11	21	91.7	84.0 to 95.7
	1994	22	32	84.3	71.2 to 91.5
	1995	20	24	72.2	41.5 to 86.8
	1996	11	19	88.4	78.2 to 93.8
	1997	45	63	82.9	74.9 to 88.4
	1998	9	12	72.9	34.9 to 88.7
Wentworth	1993	7	17	95.2	90.1 to 97.6
	1994	5	17	94.9	89.4 to 97.5
	1995	16	22	85.1	71.1 to 92.3
	1996	6	7	75.1	22.0 to 92.0
	1997	37	47	78.7	65.5 to 86.8
	1998	8	14	60.9	11.5 to 82.8
Southern & Greater Murray	1993	0	1	99.0	87.8 to 99.9
	1994	1	10	98.7	96.2 to 99.6
	1995	14	29	95.8	92.8 to 97.5
	1996	3	16	98.5	96.5 to 99.3
	1997	9	19	94.8	90.7 to 97.1
	1998	34	41	67.5	34.5 to 83.8

Table 6.9. Number of vaccinated cases (CV), total number of cases (n) and VE estimates for children aged 9–13 years by NSW health area, 1993–1998

Health area	year	CV	n	VE (%)	95% CI (%)
Central & SE Sydney	1993	34	53	73.3	58.2 to 82.9
	1994	8	13	66.8	37.8 to 82.3
	1995	6	13	76.4	40.5 to 90.6
	1996	11	19	85.5	70.7 to 92.8
	1997	69	140	87.9	83.9 to 91.0
	1998	9	16	84.3	65.2 to 92.9
Northern Rivers	1993	5	18	94.6	88.4 to 97.5
	1994	10	69	96.5	94.7 to 97.7
	1995	16	54	95.7	93.2 to 97.3
	1996	0	3	94.7	84.4 to 98.2
	1997	9	34	96.1	93.4 to 97.7
	1998	2	4	81.7	34.5 to 94.9
Western Sydney	1993	10	17	88.1	77.0 to 93.8
	1994	10	14	77.6	58.1 to 88.0
	1995	15	22	60.2	15.7 to 81.2
	1996	14	18	83.3	68.7 to 91.1
	1997	59	83	75.5	64.2 to 83.2
	1998	12	15	61.2	6.8 to 83.8
Wentworth	1993	8	13	93.1	85.8 to 96.6
	1994	9	11	92.7	84.7 to 96.5
	1995	16	20	78.6	58.4 to 89.0
	1996	12	13	64.3	-11.4 to 88.5
	1997	65	78	69.4	51.0 to 80.9
	1998	49	50	44.0	-25.0 to 74.9
Southern & Greater Murray	1993	0	1	98.6	82.5 to 99.9
	1994	3	9	98.1	94.5 to 99.4
	1995	22	38	94.0	89.8 to 96.5
	1996	7	15	97.8	95.0 to 99.0
	1997	16	26	92.6	86.7 to 95.9
	1998	60	63	53.4	6.4 to 76.8

Age group

Age group was highly significant in the base model (χ^2_3 =12.7, p=0.005). The 8-23 month age group had the lowest parameter estimate (corresponding to the highest VE estimate). The VE estimate, after adjustment for area and year, was highest in the 8–23 month age group and lowest in the 9–13 year group (*Table 6.10*).

Table 6.10. VE estimates by age group, adjusted for year and NSW health area, 1993–1998

Age group	Vaccinated cases n (PCV %)	Total cases n	VE (%)	95% CI (%)
8–23 months	191 (34)	370	96.3	94.2 to 97.5
24 years	408 (32)	849	92.7	90.3 to 94.5
5–8 years	62 (27)	165	93.9	92.5 to 95.1
9–13 years	566 (38)	942	91.3	89.2 to 92.9

Health area and year of onset

Health area was the most significant term in the base model (χ^2_4 =101, p<0.0001), followed by year of onset (χ^2_5 =32, p<0.0001). The interaction between year and area was also highly significant (χ^2_{20} =74, p<0.0001). In the base model, the parameter estimates for all the metropolitan areas (Central & South Eastern Sydney, Western Sydney and Wentworth) were not significantly different from one another. Similarly, the estimates for the rural health areas (Northern Rivers, Greater Murray and Southern) were not significantly different from one another but the rural estimates were significantly lower (ie, higher VE) than the metropolitan areas (p<0.0001). The VE estimates, adjusted for year, were higher in rural areas and lower in metropolitan areas (*Table 6.11*).

Table 6.11. Number of vaccinated cases (CV), total number of cases (n) and
VE estimates by age and NSW health area, adjusted for year, 1993–1998

Age group and area	CV	n	VE (%)	95% CI (%)
8–23 months				
Central & SE Sydney	14	32	91.6	86.6 to 94.8
Western Sydney	10	47	90.0	84.1 to 93.7
Wentworth	20	37	91.4	85.9 to 94.8
Northern Rivers	10	24	97.6	95.5 to 98.7
Southern & Greater Murray	8	25	97.9	96.7 to 98.7
2–4 years				
Central & SE Sydney	47	91	83.7	76.5 to 88.6
Western Sydney	31	104	80.4	72.0 to 86.3
Wentworth	49	78	83.2	75.2 to 88.7
Northern Rivers	43	64	95.4	91.9 to 97.3
Southern & Greater Murray	21	33	96.0	93.0 to 97.7
5–8 years				
Central & SE Sydney	109	197	86.3	81.5 to 89.9
Western Sydney	41	241	83.6	77.9 to 87.8
Wentworth	118	171	85.9	80.1 to 90.0
Northern Rivers	79	124	96.1	93.3 to 97.7
Southern & Greater Murray	61	116	96.6	94.3 to 98.0
9–13 years				
Central & SE Sydney	137	254	80.4	73.6 to 85.4
Western Sydney	42	182	76.5	68.1 to 82.7
Wentworth	120	169	79.9	71.7 to 85.7
Northern Rivers	159	185	94.4	90.4 to 96.7
Southern & Greater Murray	108	152	95.2	91.9 to 97.1

In the base model, the parameter estimates for the years 1993–1997 were not significantly different from one another but were significantly lower (ie, higher VE) than the 1998 estimate (p<0.0001). Within each age group, the differences in VE estimates between health areas were greater in 1998 than in any other year (*Tables 6.5–6.8*). The 1998 VE estimates were considerably lower than the 1996 and 1997 estimates (*Table 6.4*). However,

the 95% confidence intervals of the unadjusted VE estimates for the years 1997 and 1998 overlapped in all areas except Southern/Greater Murray, for all age groups (*Tables 6.6 – 6.9*). The VE estimates in 1998 in the Greater Murray/Southern area were significantly lower than the 1997 estimates, for all age groups. VE estimates by year, adjusted for area, were also calculated (*Table 6.12*).

Table 6.12. Number of vaccinated cases (CV), total number of cases (n) and VE estimates by age and year, adjusted for NSW health area, 1993–1998

Age group and year	CV	n	VE (%)	95% CI (%)
8–23 months				
1993	4	19	99.1	98.7 to 99.4
1994	14	33	98.9	98.4 to 99.3
1995	5	25	97.0	95.6 to 98.0
1996	5	19	98.8	97.8 to 99.3
1997	26	54	96.7	94.7 to 97.9
1998	8	15	82.4	69.5 to 89.9
2–4 years				
1993	19	44	98.3	97.8 to 98.7
1994	32	76	97.8	97.2 to 98.3
1995	34	58	94.2	92.4 to 95.5
1996	14	32	97.6	96.1 to 98.5
1997	63	124	93.5	90.7 to 95.4
1998	29	36	65.7	45.2 to 78.6
5–8 years				
1993	57	101	98.6	98.3 to 98.8
1994	63	180	98.2	97.8 to 98.5
1995	65	147	95.1	94.1 to 95.9
1996	30	70	98.0	96.8 to 98.7
1997	135	271	94.5	92.6 to 95.9
1998	58	80	71.3	55.7 to 81.4
9–13 years				
1993	57	102	97.9	97.5 to 98.3
1994	40	116	97.4	96.9 to 97.8
1995	75	147	93.0	91.7 to 94.1
1996	44	68	97.1	95.5 to 98.1
1997	218	361	92.1	89.5 to 94.1
1998	132	148	58.8	37.2 to 73.0

Alternative models

Epidemic versus non-epidemic years

The model where the variable year was substituted with the variable period, which grouped 1993 and 1997 together (the 'epidemic years') and 1994, 1995, 1996 and 1998 together (the 'non-epidemic years'), was a poorer fit. Period was not significant (χ^2_1 =1.89, p=0.17).

Metropolitan versus rural areas

In view of the finding that both the rural areas and the metropolitan areas had similar parameter estimates which were different from each other, a simplified model was run in which area had only two categories — metropolitan or rural. This model, which included the four age groups, year of disease onset, the two areas and the interaction between area and year, had a deviance of 191 with 105 df (deviance/df = 1.82). It was re-scaled in the same way as the earlier model and all the terms had p-values <0.01. In all age groups for the years 1993 to 1997, VE estimates were higher in the rural area than in the metropolitan area but in 1998 the situation was reversed, with the rural area having lower VE estimates than the metropolitan areas (*Tables 6.13 to 6.16*). After adjusting for year, the rural area had higher VE estimates than the metropolitan area (*Table 6.17*).

Table 6.13. Number of vaccinated cases (CV), total number of cases (n) and VE estimates for children aged 8–23 months in NSW metropolitan and rural areas by year, 1993–1998

Area	year	CV	n	VE (%)	95% CI (%)
Metropolitan	1993	17	36	92.6	86.8 to 95.9
	1994	19	34	91.3	84.1 to 95.3
	1995	23	28	88.0	76.7 to 93.9
	1996	10	18	92.2	85.2 to 95.9
	1997	51	94	92.2	87.2 to 95.3
	1998	19	23	85.4	71.2 to 92.6
Rural	1993	2	8	98.0	94.8 to 99.2
	1994	13	42	98.6	97.4 to 99.3
	1995	11	30	97.9	96.2 to 98.8
	1996	4	14	98.7	96.9 to 99.5
	1997	12	30	97.8	95.9 to 98.8
	1998	10	13	83.3	62.3 to 92.6

Table 6.14. Number of vaccinated cases (CV), total number of cases (n) and VE estimates for children aged 2–4 years in NSW metropolitan and rural areas by year, 1993–1998

Area	year	CV	n	VE (%)	95% CI (%)
Metropolitan	1993	52	85	86.3	78.3 to 91.4
	1994	47	80	83.9	73.4 to 90.3
	1995	40	51	77.7	60.8 to 87.4
	1996	25	44	85.5	74.6 to 91.8
	1997	119	196	85.5	79.4 to 89.9
	1998	23	36	72.8	50.9 to 85.0
Rural	1993	5	16	96.3	90.9 to 98.5
	1994	16	100	97.4	95.7 to 98.5
	1995	25	96	96.0	93.6 to 97.5
	1996	5	26	97.7	94.7 to 99.0
	1997	16	75	95.9	93.1 to 97.5
	1998	35	44	68.9	34.9 to 85.2

Table 6.15. Number of vaccinated cases (CV), total number of cases (n) and VE estimates for children aged 5–8 years in NSW metropolitan and rural areas by year, 1993–1998

Area	year	CV	n	VE (%)	95% CI (%)
Metropolitan	1993	3	10	88.1	82.3 to 92.0
	1994	10	15	86.0	78.2 to 91.1
	1995	4	9	80.7	67.3 to 88.6
	1996	4	14	87.4	79.0 to 92.5
	1997	19	35	87.4	83.4 to 90.5
	1998	4	10	76.4	59.0 to 86.4
Rural	1993	1	9	96.8	92.3 to 98.7
	1994	4	18	97.8	96.4 to 98.6
	1995	1	16	96.6	94.8 to 97.7
	1996	1	5	98.0	95.5 to 99.1
	1997	7	19	96.4	94.3 to 97.7
	1998	4	5	73.0	45.7 to 86.6

Table 6.16. Number of vaccinated cases (CV), total number of cases (n) and VE estimates for children aged 9–13 years in NSW metropolitan and rural areas by year, 1993–1998

Area	year	CV	n	VE (%)	95% CI (%)
Metropolitan	1993	52	83	83.0	74.5 to 88.6
	1994	27	38	80.0	67.9 to 87.5
	1995	37	55	72.3	53.1 to 83.6
	1996	37	50	82.0	69.9 to 89.2
	1997	193	301	82.0	76.7 to 86.1
	1998	70	81	66.1	42.0 to 80.2
Rural	1993	5	19	95.4	89.0 to 98.1
	1994	13	78	96.8	94.9 to 98.0
	1995	38	92	95.1	92.6 to 96.7
	1996	7	18	97.1	93.6 to 98.7
	1997	25	60	94.8	91.8 to 96.7
	1998	62	67	61.3	22.4 to 80.7

Table 6.17. Number of vaccinated cases (CV), total number of cases (n) and VE estimates by age group in NSW metropolitan and rural areas, adjusted for year, 1993–1998

Age group	Area	CV	n	VE (%)	95% CI (%)
8-23 months	Metropolitan	44	93	90.6	85.0 to 94.2
	Rural	18	72	97.4	95.5 to 98.5
2 – 4 years	Metropolitan	139	233	82.6	75.9 to 87.4
	Rural	52	137	95.3	93.1 to 96.7
5 – 8 years	Metropolitan	306	492	84.9	80.8 to 88.1
	Rural	102	357	95.9	94.4 to 96.9
9 – 13 years	Metropolitan	416	608	78.3	72.5 to 82.9
	Rural	150	334	94.1	92.0 to 95.6

Pooled regional population estimates

The final model using the pooled PPV estimate had the same deviance as the model in which PPV for each area was used, but health area accounted for more of the variability (in the base model, χ_4^2 was 271 compared with 232, p<0.0001 in both cases). Areas with lower PPV than the pooled estimate of 0.93 generally had higher VE estimates and *vice versa*.

Changes in population coverage

The model which used the higher PPV values (*Table 6.4*) had the same fit as the original model. The VE estimates for all ages, areas and years were higher with the greatest increase seen in the 1998 estimates (Appendix 6.1).

Changes in case definition

4 doses

Requiring cases aged over 18 months to have received 4 doses of the vaccine to be considered fully vaccinated and excluding cases in this age group who had received only 3 doses resulted in 2207 cases, 1108 (50%) of whom were vaccinated. The model was similar to the original model although it was a slightly poorer fit (deviance=122 on 87 df). VE estimates were slightly higher than the original estimates (Appendix 6.2).

Including partially vaccinated in the unvaccinated group

Classifying partially vaccinated (1 or 2 doses) as unvaccinated resulted in 2447 cases, 1108 (45%) of whom were vaccinated. The model was a marginally better fit than the original model (deviance=108 on 87 df) and the same explanatory variables were still highly significant (p<0.01). VE estimates from this model, adjusted for year and health area (*Table 6.18*) and the individual estimates (Appendix 6.3) were considerably lower.

Table 6.18. VE estimates by age group, adjusted for year and NSW health area (partially vaccinated classified as unvaccinated), 1993–1998

Age group	Vaccinated cases (PCV %)	Total cases	VE (%)	95% CI (%)
8–23 months	60	181	91.4	87.3 to 94.2
2–4 years	165	386	86.4	82.2 to 89.7
5–8 years	376	900	86.8	83.9 to 89.2
9–13 years	507	980	82.6	80.6 to 84.5

Laboratory confirmed cases

After excluding partially vaccinated cases and those of unknown vaccination status, there were 1713 laboratory confirmed cases, 903 of whom were vaccinated. The final model with all the explanatory variables was a better fit than the base model which did not require laboratory confirmation (deviance 98.8 with 83 df). Overall, VE estimates based on laboratory confirmed cases were higher than when all notified cases were included, although there was some individual variation (Appendix 6.4). Some combinations of age groups, areas and years did not have any notified cases and so VE for these combinations could not be calculated. As in the other models, the rural areas had higher VE estimates than the metropolitan areas (*Table 6.19*) and 1998 had the lowest VE estimates (*Table 6.20*). After adjusting for area and year, VE in all age groups was 99% (*Table 6.21*). However, the parameter estimate for 1993 was at least 10 times lower than for the other years, so averaging the parameter estimates for year masks the differences between years.

Table 6.19. Number of vaccinated cases (CV), total number of cases (n) and VE estimates by age and NSW health area, adjusted for year, 1993–1998

Age group and area	CV	n	VE (%)	95% CI (%)
8–23 months				
Central & SE Sydney	3	12	94.7	90.1 to 97.1
Western Sydney	12	24	93.1	87.6 to 96.1
Wentworth	8	18	94.0	89.7 to 96.5
Northern Rivers	4	22	98.5	97.1 to 99.2
Southern & Greater Murray	3	16	99.9	99.9 to 100
2–4 years				
Central & SE Sydney	15	37	87.8	80.6 to 92.4
Western Sydney	31	49	84.1	75.9 to 89.6
Wentworth	28	46	86.3	80.8 to 90.2
Northern Rivers	15	67	96.5	94.4 to 97.9
Southern & Greater Murray	17	26	99.9	99.8 to 99.9
5–8 years				
Central & SE Sydney	56	116	87.8	82.3 to 91.6
Western Sydney	88	126	84.1	78.0 to 88.5
Wentworth	67	101	86.3	82.6 to 89.2
Northern Rivers	28	181	96.5	94.7 to 97.7
Southern & Greater Murray	51	89	99.9	99.8 to 99.9
9–13 years				
Central & SE Sydney	101	182	80.5	72.1 to 86.3
Western Sydney	102	143	74.5	64.5 to 81.7
Wentworth	141	167	78.0	68.7 to 84.5
Northern Rivers	36	163	94.4	91.5 to 96.3
Southern & Greater Murray	97	128	99.8	99.7 to 99.9

Table 6.20. Number of vaccinated cases (CV), total number of cases (n) and VE estimates by age and year, adjusted for NSW health area, 1993–1998

Age group and year	CV	n	VE (%)	95% CI (%)
8–23 months				
1993	1	7	100	99.9 to 100
1994	4	18	96.5	92.8 to 98.3
1995	3	15	95.1	90.9 to 97.4
1996	3	13	95.9	92.0 to 97.9
1997	14	30	96.1	89.1 to 98.6
1998	5	9	88.1	76.8 to 93.9
2–4 years				
1993	9	27	99.9	99.8 to 99.9
1994	17	49	91.9	85.6 to 95.5
1995	16	36	88.8	81.9 to 93.0
1996	9	19	90.7	84.1 to 94.6
1997	35	68	91.0	77.1 to 96.5
1998	20	26	72.8	53.6 to 84.0
5–8 years				
1993	33	59	99.9	99.8 to 99.9
1994	41	132	91.9	86.4 to 95.2
1995	50	105	88.7	83.3 to 92.4
1996	21	51	90.7	85.0 to 94.2
1997	94	196	91.0	77.9 to 96.3
1998	51	70	72.7	56.2 to 83.0
9–13 years				
1993	38	70	99.8	99.7 to 99.9
1994	35	103	87.0	78.2 to 92.3
1995	62	122	81.9	73.6 to 87.6
1996	40	58	85.0	76.1 to 90.7
1997	183	298	85.6	80.1 to 89.5
1998	119	132	56.3	30.7 to 72.4

Table 6.21. Age group: test statistics, number of vaccinated cases (CV), total number of cases (n) and VE for laboratory confirmed cases, 1993–1998

Age group	CV	n	χ^2	P-value	VE (%)	95% CI (%)
8–23 months	30	92	20.3	<0.0001	99.9	99.8 to 99.9
2–4 years	106	225	6.1	0.01	99.7	99.6 to 99.8
5–8 years	290	613	11.6	0.0007	99.7	99.7 to 99.8
9–13 years	477	783	referent		99.6	99.5 to 99.6

Discussion

This study shows that pertussis vaccination is highly effective at preventing pertussis in NSW children, as measured by notified cases. The VE estimates presented here are really estimates of the effectiveness of pertussis vaccination at preventing pertussis notification, rather than disease *per se*. As we have no data on non-notified cases we are unable to determine the extent to which the VE estimates reflect the effectiveness of preventing pertussis infection or disease of differing severity due to pertussis infection. The estimates in this study are not vaccine-specific but largely represent whole-cell vaccines, as acellular pertussis vaccines have only been available free of charge for use in the primary course since February 1999.[12] Although acellular vaccines were available in NSW prior to 1999, the proportion used was small (see Chapter 4) and infants who received all three doses of an acellular vaccine in 1998 would not be of an eligible age for this study until 1999.

Although this study aimed to measure the effectiveness of three doses of a pertussis-containing vaccine, most cases who had received three doses and were eligible for a fourth dose had received it. Assuming that four doses of the vaccine are more effective than three doses, the effectiveness of three doses may have been over-estimated. Not surprisingly, excluding cases aged over 18 months who had not received four or more doses of the vaccine increased the VE estimate. This increase was quite small, which is to be expected, as only 119 of the 2326 (5%) cases were excluded on the basis of this definition change. Half the 5–8 year old age group had received a fifth dose. In the future we would expect this proportion to rise with a corresponding increase in the VE estimate, both overall and relative to the 9–13 year olds.

Classifying partially vaccinated cases as unvaccinated had the effect of lowering the VE estimates. This is expected as partial vaccination against pertussis gives some protection against disease, thus reducing the risk of disease in the unvaccinated group. These estimates, which compare the risk of disease in the fully vaccinated with those partially vaccinated or unvaccinated, demonstrate the effectiveness of completing the primary vaccination schedule for pertussis versus not completing the schedule. In some countries and areas information on partial vaccination is not available and this is the only method of classification. Such is the case in New Zealand, so classifying cases this way allows comparison with the New Zealand VE estimates.[5] The 1996 and 1997 VE estimates are similar to those reported in a New Zealand study which applied the screening method to notification data from the 1996 pertussis epidemic, although our estimates are higher in the youngest age group and lower in the 2–4 year olds.[5]

Including only cases in whom pertussis is laboratory confirmed increases the specificity of the case definition. Previous studies have found that increasing the specificity by including only clinically severe or culture positive cases has increased the VE estimates.[7,13] In this study, including only laboratory confirmed cases did not have a big effect. This may be because 73% of the cases in the study were laboratory confirmed, a finding not surprising as laboratory confirmed cases are more likely to be notified. In addition, many of the notifications which are recorded as being notified on clinical grounds are likely to be severe cases.

Possible sources of bias

Possible sources of bias and the likely effect on VE estimates are summarised in *Table 6.22*.

Cases

Cases with unknown vaccination status give rise to a potential selection bias. It is possible that cases who were not as readily followed-up to check their vaccination status were less likely to be fully vaccinated than cases who were able to be followed-up. However, excluding health areas where the vaccination status of a large proportion of cases was unknown minimises this bias. In health areas where vaccination status was known for at least 75% of notifications, the PCV was higher, resulting in lower VE estimates. If PCV in excluded areas was really lower (ie, if the distribution of vaccination status was similar

amongst those in whom it was unknown to what it was for those in whom it was known) and these areas were included, then the VE estimates would have been higher.

It was not feasible for this study to validate vaccination status. As parental recall generally overestimates vaccination coverage, vaccination status of cases is more likely to be misclassified as vaccinated.[14] This would lead to an underestimate of VE. There could be variation in the way information on vaccination status is collected between health areas and/or over time. For the later notifications, and in the future, it is possible for public health units to check the vaccination status of a notified case on the ACIR.

Information on the date of vaccination was not available. Some cases, particularly among eight and nine month olds, may have been vaccinated just prior to disease onset and hence there may have been insufficient time between vaccination and disease onset for development of an immunologic response. This might have been a greater problem if six and seven month old cases had been included. Although ideally these cases should be excluded, the effect (if any) is likely to be small. Firstly, most infants have completed the primary schedule by seven and a half months (see Chapter 4) and secondly, eight and nine month old infants comprise less than two percent of cases.

Pertussis tends to be much milder in vaccinated than non-vaccinated cases, and milder cases are less likely to be diagnosed and notified. This has the effect of increasing VE estimates and what is being measured is the effectiveness of vaccination at preventing more serious illness. Ramsay et al,[3] who used the screening method to estimate pertussis VE in the UK, found that estimates were generally lower in the epidemic period than in non-epidemic periods. The authors offered two possible explanations for this. The first explanation is related to the increased reporting in epidemics of milder cases, who are more likely to be vaccinated, leading to an increased proportion of vaccinated cases. The alternate explanation is that protection by vaccination is less during periods of heavy exposure. Guris et al,[4] who used the screening method to determine the effectiveness of the pertussis vaccination program in the United States from 1992 to 1994, reported the highest VE estimate in 1992. In 1993 and 1994 large outbreaks of pertussis were reported and the authors suggested the same explanations. The VE estimates in our study were not lower in epidemic years. However, it is possible that local outbreaks with subsequent increased

awareness of pertussis were responsible for some of the regional differences in VE estimates.

Where VE estimates are derived from notifications, detection bias (ie, the tendency to suspect pertussis less in persons known to be fully vaccinated) is an important potential problem leading to falsely high VE estimates.[3] Although it was not possible to determine the importance of this bias in NSW notifications, with the exception of possible increased reporting during epidemics, one would expect its effect to be constant over time.

Coverage estimates

The ACIR did not commence operation until January 1996, so coverage data were not available for all years in the study period. The cohort used for estimation of PPV was chosen in preference to earlier cohorts to allow time for improvement in reporting of vaccinations to the ACIR. There are no other sources of vaccination status of children by health area. The only comprehensive study to estimate the percentage of NSW children in receipt of three doses of a pertussis-containing vaccine, with which the ACIR data can be compared, is the 1995 Australian Bureau of Statistics (ABS) survey.[15] The ABS 1995 survey estimated that 87% of NSW children aged 12 months had received 3 doses of DTP vaccine.[16] A study conducted in northern Sydney in 1992 found that 86% of respondents (response rate 58%) stated that their child was fully vaccinated.[17] In Northern Sydney, 84% of the cohort selected from the ACIR for this study had received 3 doses of DTP. These findings are consistent with the PPV values we used in the model. However, a NSW vaccination coverage survey conducted in 1992 found that, of 264 children aged 6–24 months, only 62% could provide evidence of 3 doses of a pertussis-containing vaccine from a parent-held child health record.[18] It is likely that PPV was over-estimated for the early part of the study period, hence VE for the earlier years and for the older age groups was over- estimated. In view of this, re-analyses of the data for the years 1996–1998 (ie, excluding 1993–1995) were undertaken and the results are presented in Part B of this chapter. It should be noted that the PPV values were incorporated into the model as fixed values, therefore the confidence intervals only relate to the error of the linear predictor and do not incorporate any error around the PPV values.

Underestimation of vaccination coverage will reduce VE estimates. The ACIR data most likely underestimate true current coverage due to incomplete reporting of vaccination

status. In 1998 it was estimated that 50% or more children who were recorded on the ACIR as incompletely vaccinated were in fact fully vaccinated.[15] The effect of increasing the population estimates was seen to raise the VE estimates. However, if coverage has improved over the study period, then the ACIR estimates used may have overestimated coverage in the earlier part of the study period and in the older age groups. True coverage may have increased as a number of incentive schemes have been introduced by the Commonwealth Government since 1997.[19] This may be at least partly responsible for the apparently lower VE in 1998. Reporting to the ACIR may vary between health areas and could account for some of the regional differences in VE estimates. Coverage may have improved over the study period differentially between areas, which could explain the significance of the interaction between health area and year.

Table 6.22. Potential sources of bias and the likely effect on VE estimates

Potential source of bias	Effect on VE estimate*
Cases with unknown vaccination status more likely to be unvaccinated	↓
Non-differential misclassification of cases	↓
Unvaccinated cases more likely to be misclassified as vaccinated	↓↓
PPV underestimated (most likely in the latter years and younger age groups)	↓
Inclusion of cases who were vaccinated in the 2 weeks prior to disease onset	↓ (small)
Vaccinated cases more likely to be notified due to better access to health care	↓
Severe or typical cases who are more likely to be unvaccinated are more likely to be notified	↑
Unvaccinated cases more likely to be notified	↑↑
PPV overestimated (most likely for earlier years and in older age groups)	↑↑

*↓ indicates the bias would reduce the VE estimate and if it occurred the calculated VE estimations under-estimate true VE.

Age

VE estimates were consistently highest in the youngest age group and lowest in the oldest age group. If, as we suspect, PPV values were lower than those used in these analyses in

the oldest age groups then the true VE estimates would be even lower in these groups. Age is a proxy measure for time since vaccination and if vaccine-acquired immunity wanes with time then we would expect VE to be lowest in the older children. Although older children have a greater probability of having been exposed to the disease and therefore of having had the disease, the proportion of the population who have had the disease is relatively small and so the effect, if any, would be small. These results, together with the increasing rates of notified 10–14 year old cases in Australia (Chapters 2 & 3), suggest that childhood vaccination against pertussis is less effective against disease in adolescence.

Area

Much of the variation in VE between areas could be due to inaccuracies in PPV estimates for some or all of the study period. The use of pooled PPV figures in the model instead of individual figures for each health area increased the variation in VE between areas even further. However, differences in notification practices, handling and storage of vaccines and levels of exposure to pertussis may also account for some of the differences in VE. In addition, awareness of pertussis activity, for example local outbreaks, may affect the likelihood of suspicion, diagnosis and notification of pertussis.

The reason VE estimates are consistently higher in rural than metropolitan areas is not clear. It may be that population coverage has increased more in rural areas than in metropolitan areas since the start of the study period. The finding that the difference between rural and metropolitan areas is less in 1998 than in previous years supports this suggestion. Alternatively, there may be less exposure in less densely populated rural areas and the vaccine may be less effective under conditions of heavy exposure, which may be more likely to be found in metropolitan areas.

Year

The VE estimates for cases with disease onset in 1998 were generally lower than for other years, particularly in the Southern/Greater Murray area. The population coverage figures used in the model may be a more accurate reflection of true PPV in 1998 than in previous years. If this is the case, then the 1998 VE estimates are more realistic than those for 1996 and 1997. A study using similar methodology in the United States estimated pertussis VE between 1994 and 1996 in 7–18 month old children to be 82%,[4] the same as our 1998 estimate in the youngest age group. Alternatively, coverage may have improved over the

three-year period with coverage being underestimated for 1998, thus resulting in an underestimate of VE in 1998. The most likely scenario lies somewhere in between these two alternative explanations — that is, coverage has improved and was over-estimated for the years 1996 and 1997 and under-estimated for 1998.

The possibility that VE did actually decrease in 1998 should not be completely dismissed. A recent paper from The Netherlands reported a downward trend in VE and in 1997, the final year in which VE was analysed, the PCV exceeded the PPV.[1] The authors suggested two possible explanations for this. The first is that there may be a mismatch of the vaccine strain and the circulating *Bordetella pertussis* strains; the second is that the lower immunogenicity profile of the Dutch vaccine may have resulted in greater vulnerability to antigenic changes in *Bordetella pertussis*.[1] Although there is no evidence to suggest that this is the case in Australia, the ongoing surveillance of pertussis including VE is of paramount importance.

It is also possible that differences in VE over the time period were due to differences in notification practices, although we have no evidence of changes to the notification system. A UK study found that pertussis VE was significantly lower during epidemic than non-epidemic periods.[3] However, 'epidemic period' was not significant in our model and the VE estimates were lower in 1998, which was a 'non-epidemic' period.

Other potentially confounding variables

Other variables may be independently related to both the risk of being notified with pertussis and to vaccination status and thus confound the VE estimate. Unlike randomised controlled trials, where potential confounding variables, both known and unknown, are randomly distributed among the experimental and control groups, we can only control for other potential confounders if we have information on them, which in this study we do not. Other potential confounding variables may include socioeconomic status, level of education, ethnicity and attendance at institutions such as childcare.

Conclusion

Although the extent to which notified childhood cases of pertussis represent all childhood cases of pertussis is not known, the results of this study suggests that the pertussis vaccination program is highly effective, especially in younger children. Whilst the potential

for bias in this study would be unacceptable in many studies, trends in VE may still be monitored provided any bias remains constant over time. The strength of this methodology lies in its ease of application and the fact that it could be incorporated into routine surveillance of vaccine preventable diseases.

As the ACIR matures, checking the immunisation status of cases will be easier and the population estimates more accurate. In addition, it will be possible to use the population coverage data of the cohort of children from which the cases arose, which will improve the precision of the VE estimates. In contrast to the previous studies which have used the screening method to estimate pertussis VE,[1-5] we have been able to use regional coverage data. The United Kingdom study is the only previous study which has used a logistic regression model and, whilst it stratified by year and age, it did not stratify by area.[3] The authors comment that the use of national coverage data may produce artificially high VE estimates[3] and Farrington illustrates the confounding effect of pooling population coverage data.[9] In Australia, regional coverage data are available from the ACIR and should be used in all future pertussis VE studies which use the screening method.

A review of vaccine preventable diseases in Australia from 1993 to 1998 found that pertussis was responsible for more morbidity than any other vaccine preventable disease and that the nine deaths recorded in the years from 1993 to 1997 equalled the number in the previous decade.[12] Reducing the morbidity associated with pertussis requires an understanding of the disease epidemiology in the population. Much of this understanding comes from notification data. The documentation of vaccination status of notified cases who would have been eligible for vaccination at the time of disease onset is essential for program evaluation and planning. The impact of the change to acellular pertussis vaccine and changes to the schedule must be monitored — such monitoring will assist future vaccine policy decisions.

Part B: Effectiveness of pertussis vaccination in NSW children, 1996 to 1998

Background

The results of the previous study (Part A) suggest that PPV had been overestimated for the earlier years of the study period. As there are no data which measure population coverage by health area for the years 1993 to 1995, in this part of the study these years were excluded.

Methods

The methods are identical to the previous study except that dates of onset prior to 1 January 1996, were excluded from analyses. The effect of excluding Southern/Greater Murray Health areas was examined, as was the effect of excluding the 9–13 year age group.

Results

Fitting the model

The model with no explanatory variables remained a poor fit (deviance=240 with 59 df) but was still a better fit than the equivalent model in the previous study. The addition of each explanatory variable by itself significantly improved the fit of the model (*Table 6.23*). Health area was the most significant explanatory variable. All variables remained significant in the model in which all three were included ($p<0.0001$).

Table 6.23. Summary of models

Explanatory variable(s)	Dev*/ df[†]	χ^2	df	p-value
None	4.06			
Age	3.70	32	3	<0.0001
Year	3.38	47	2	<0.0001
Area	2.54	100	4	<0.0001
Age + year + area	1.49			
Age + year + area + year*area	1.11			
Age + year + area + year*area (excluding 9-13 year olds)	0.95			

*Dev=deviance

[†]df=degrees of freedom.

The final model included age group, year of onset and area (base model) plus the interaction between area and year. This model had a deviance of 46 with 42 degrees of freedom suggesting that the model fitted the data (p=0.3), therefore there was no need to re-scale the model. In the final model all variables were significant (p<0.001). Although still significant, health area, year and the interaction between area and year explained less of the variability than when all years were included.

VE Estimates

VE estimates from the final model for each of the four age groups, stratified by health area and year, can be seen in *Tables 6.24 to 6.27*.

Table 6.24. Number of vaccinated cases (CV), total number of cases (n) and VE estimates for children aged 8–23 months by health area, 1996–1998

Area	year	CV	n	VE (%)	95% CI (%)
Central & SE Sydney	1996	1	4	93.7	86.7 to 97.0
	1997	4	13	94.8	91.2 to 96.9
	1998	0	3	93.2	84.6 to 97.0
Northern Rivers	1996	1	2	97.6	93.1 to 99.1
	1997	3	11	98.3	96.7 to 99.1
	1998	2	2	91.8	73.4 to 97.5
Western Sydney	1996	1	6	92.6	85.2 to 96.3
	1997	8	12	89.2	81.4 to 93.7
	1998	4	6	82.9	60.2 to 92.7
Wentworth	1996	2	4	84.6	55.6 to 94.6
	1997	7	10	86.7	75.9 to 92.7
	1998	0	1	75.9	43.9 to 89.6
Southern & Greater Murray	1996	0	3	99.0	97.8 to 99.6
	1997	4	8	96.8	93.8 to 98.3
	1998	2	3	79.7	56.6 to 90.5

Table 6.25. Number of vaccinated cases (CV), total number of cases (n) and VE estimates for children aged 2–4 years by health area, 1996–1998

Area	year	CV	n	VE (%)	95% CI (%)
Central & SE Sydney	1996	1	2	89.2	78.5 to 94.6
	1997	21	47	91.0	86.9 to 93.8
	1998	2	4	88.3	75.2 to 94.5
Northern Rivers	1996	3	9	95.8	89.2 to 98.4
	1997	5	19	97.0	94.9 to 98.3
	1998	2	4	86.0	56.6 to 95.5
Western Sydney	1996	8	14	87.2	76.8 to 92.9
	1997	20	32	81.5	71.8 to 87.9
	1998	5	6	70.7	34.2 to 86.9
Wentworth	1996	1	2	73.5	25.2 to 90.6
	1997	10	15	77.2	62.2 to 86.2
	1998	12	13	58.6	12.1 to 80.5
Southern & Greater Murray	1996	1	5	98.3	96.4 to 99.2
	1997	7	11	94.4	90.1 to 96.9
	1998	8	9	65.1	31.2 to 82.3

Table 6.26. Number of vaccinated cases (CV), total number of cases (n) and VE estimates for children aged 5–8 years by health area, 1996–1998

Area	year	CV	n	VE (%)	95% CI (%)
Central & SE Sydney	1996	8	18	90.6	82.4 to 95.0
	1997	37	86	92.2	89.4 to 94.2
	1998	6	10	89.8	79.3 to 95.0
Northern Rivers	1996	2	10	96.4	90.6 to 98.6
	1997	7	56	97.4	95.9 to 98.4
	1998	1	3	87.8	62.4 to 96.0
Western Sydney	1996	11	19	88.9	80.5 to 93.7
	1997	45	63	83.9	77.0 to 88.7
	1998	9	12	74.5	44.6 to 88.2
Wentworth	1996	6	7	76.9	37.0 to 91.6
	1997	37	47	80.1	69.3 to 87.1
	1998	8	14	63.9	25.4 to 82.6
Southern & Greater Murray	1996	3	16	98.6	97.0 to 99.3
	1997	9	19	95.2	91.7 to 97.2
	1998	34	41	69.6	43.6 to 83.6

Table 6.27. Number of vaccinated cases (CV), total number of cases (n) and VE estimates for children aged 9–13 years by health area, 1996–1998

Area	year	CV	n	VE (%)	95% CI (%)
Central & SE Sydney	1996	11	19	84.4	70.9 to 91.6
	1997	69	140	87.0	83.0 to 90.0
	1998	9	16	83.1	65.9 to 91.6
Northern Rivers	1996	0	3	94.0	84.3 to 97.7
	1997	9	34	95.7	93.1 to 97.4
	1998	2	4	79.7	37.8 to 93.4
Western Sydney	1996	14	18	81.5	67.5 to 89.5
	1997	59	83	73.2	62.0 to 81.1
	1998	12	15	57.6	8.0 to 80.5
Wentworth	1996	12	13	61.7	-4.1 to 85.9
	1997	65	78	67.0	49.5 to 78.4
	1998	49	50	40.1	-21.5 to 70.4
Southern & Greater Murray	1996	7	15	97.6	95.1 to 98.8
	1997	16	26	91.9	86.4 to 95.2
	1998	60	63	49.5	6.4 to 72.8

Age group

Age group was highly significant in the base model $\chi^2_3 = 20$, p<0.0001). The 8–23 month age group had the lowest parameter estimate (corresponding to the highest VE estimate). The VE estimate, after adjustment for area and year, remained highest in the 8 to 23 month age group and lowest in the 9–13 year group (*Table 6.28*). The relative magnitude of the parameter estimates was unchanged when the 9–13 year group was excluded from analyses, but the base model was a better fit (*Table 6.23*) and age group was no longer significant ($\chi^2_2 = 3.4$, p=0.18).

Table 6.28. Age group: test statistics, number of vaccinated cases (CV), total number of cases (n) and VE estimates

	CV	n	χ^2	P-value	VE (%)*	95% CI (%)
8 to 23 month olds	39	80	12.4	0.0004	91.0	85.5 to 94.4
2 to 4 year olds	106	192	3.78	0.052	84.5	78.3 to 88.9
5 to 8 year olds	223	421	11.8	0.0006	86.5	82.7 to 89.5
9 to 13 year olds	394	577	referent		77.6	71.7 to 82.3

*Adjusted for year and health area

Health area and year of onset

As in Part A, health area was the most significant term in the base model (χ^2_4=91, p<0.0001) followed by year of onset (χ^2_2=41, p<0.0001). The interaction between year and area also remained highly significant (χ^2_8=28, p=0.0004). However, the test statistics for these three terms were lower, with corresponding higher p-values. There was not a clear metropolitan/rural divide as in Part A of the study. In the base model, the parameter estimates for Western Sydney and Wentworth were not significantly different from one another whilst the estimates for Northern Rivers, Greater Murray, Southern and Central and South Eastern Sydney were not significantly different from one another, but the latter estimates were significantly lower (ie, higher VE — *Table 6.29*) than the former areas (p<0.0001).

As in Part A, the 1998 VE estimates, adjusted for health area, were considerably lower than the 1996 and 1997 estimates (*Table 6.30*). However, the 95% confidence intervals of the unadjusted VE estimates (*Tables 6.24–6.27*) for the years 1996 to 1998 overlapped in all areas except Southern/Greater Murray, in all age groups. When the model was run with the Greater Murray/Southern area excluded, the interaction term was no longer significant (p=0.6). Following removal of the interaction term, year accounted for less of the variability than the final model but was still significant (χ^2_2=6.3, p=0.04), with 1998 VE estimates lower than the previous years.

Table 6.29. Number of vaccinated cases, total number of cases and VE estimates by health area and age, adjusted for year, 1996–1998

Age group and area	Vaccinated cases	Total cases	VE (%)	95% CI (%)
8–23 months				
Central & SE Sydney	5	20	93.9	89.5 to 96.5
Northern Rivers	6	15	96.8	93.7 to 98.3
Western Sydney	13	16	88.9	81.1 to 93.5
Wentworth	9	15	83.0	68.8 to 90.7
Southern & Greater Murray	6	14	96.0	94.5 to 97.1
2–4 years				
Central & SE Sydney	24	53	89.6	83.8 to 93.3
Northern Rivers	10	32	94.4	90.2 to 96.8
Western Sydney	33	52	80.9	70.7 to 87.6
Wentworth	23	30	70.7	50.7 to 82.6
Southern & Greater Murray	16	25	93.1	89.1 to 95.7
5–8 years				
Central & SE Sydney	51	114	90.9	87.0 to 93.7
Northern Rivers	10	69	95.1	91.7 to 97.2
Western Sydney	65	94	83.4	76.0 to 88.5
Wentworth	51	68	74.5	59.5 to 84.0
Southern & Greater Murray	46	76	94.0	91.2 to 95.9
9–13 years				
Central & SE Sydney	89	175	84.9	78.7 to 89.3
Northern Rivers	11	41	91.9	86.2 to 95.3
Western Sydney	85	116	72.4	60.1 to 80.9
Wentworth	126	141	57.7	33.9 to 72.9
Southern & Greater Murray	83	104	90.1	85.5 to 93.2

Table 6.30. Number of vaccinated cases, total number of cases and VE estimates by year and age, adjusted for health area, 1996–1998

Age group and area	Vaccinated cases	Total cases	VE (%)	95% CI (%)
8–23 months				
1996	5	19	94.2	89.9 to 96.6
1997	26	54	93.0	88.7 to 95.7
1998	8	15	82.0	68.5 to 89.7
2–4 years				
1996	14	32	90.0	84.3 to 93.6
1997	63	124	88.0	83.1 to 91.4
1998	29	36	69.2	51.4 to 80.4
5–8 years				
1996	30	70	91.3	87.2 to 94.0
1997	135	271	89.5	86.6 to 91.8
1998	58	80	73.2	60.0 to 82.0
9–13 years				
1996	44	68	85.5	78.7 to 90.1
1997	218	361	82.6	78.1 to 86.2
1998	132	148	55.4	34.6 to 69.6

Discussion

The better fit of the model after restriction of year of onset suggests that the population estimates are a more accurate reflection of the latter years than the earlier years of the study period. This would also affect the older age groups and hence the estimates for the older age groups are likely to be lower than the calculated values. This is supported by the better fit of the model in which the 9–13 year old age group was excluded. However, even in this part of the study where the years are restricted, the VE estimates for cases with disease onset in 1998 were still lower than for other years. The PPV figures used in the model may be a more accurate reflection of true PPV in 1998 than in previous years. If this is the case, then the 1998 VE estimates are more realistic than those for 1996 and 1997. Alternatively, coverage may have improved over the three-year period with coverage being underestimated for 1998, thus resulting in an underestimate of VE in 1998.

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The significantly lower VE estimate in the Southern/Greater Murray area in 1998 compared with 1996 and 1997, together with the elimination of significant interaction upon removal of this area from the model, suggests that PPV increased more in this area than in the other areas. This, together with the finding that area and interaction between year and area is less significant in this model than in Part A, provides further evidence that some or most of the variation in VE between areas is due to inaccuracies in PPV estimates.

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Appendix 6.1

Results of sensitivity analysis: VE estimates using higher values of PPV, 1993–1998 notification data

Table A6.1.1. VE estimates for children aged 8–23 months by health area,
1993–1998

Area	year	CV	n	VE (%)	95% CI (%)
Central & SE Sydney	1993	1	3	93.2	87.7 to 96.2
	1994	6	6	91.5	82.7 to 95.8
	1995	2	3	94.0	83.8 to 97.7
	1996	1	4	96.3	91.8 to 98.3
	1997	4	13	96.9	95.0 to 98.1
	1998	0	3	96.0	90.4 to 98.3
Northern Rivers	1993	0	6	98.6	96.8 to 99.4
	1994	3	16	99.1	98.4 to 99.5
	1995	1	10	98.9	98.0 to99.4
	1996	1	2	98.7	95.8 to 99.6
	1997	3	11	99.0	98.1 to 99.5
	1998	2	2	95.3	82.6 to 98.7
Western Sydney	1993	2	3	96.9	93.5 to 98.6
	1994	4	8	94.2	88.3 to 97.1
	1995	1	2	89.7	76.3 to 95.5
	1996	1	6	95.7	91.2 to 97.9
	1997	8	12	93.7	89.3 to 96.3
	1998	4	6	90.0	74.7 to 96.0
Wentworth	1993	0	4	98.2	95.9 to 99.2
	1994	0	1	98.0	95.5 to 99.1
	1995	1	4	94.3	87.9 to 97.3
	1996	2	4	90.5	69.1 to 97.1
	1997	7	10	91.9	85.2 to 95.5
	1998	0	1	85.1	63.4 to 93.9
Southern & Greater Murray	1993	1	3	99.6	95.4 to 100
	1994	1	2	99.5	98.5 to 99.8
	1995	0	6	98.4	97.0 to 99.2
	1996	0	3	99.4	98.6 to 99.8
	1997	4	8	98.1	96.2 to 99.0
	1998	2	3	87.7	72.8 to 94.5

Table A6.1.2. VE estimates for children aged 2–4 years by health area, 1993–1998

Area	year	CV	n	VE (%)	95% CI (%)
Central & SE Sydney	1993	10	19	86.7	78.2 to 91.9
	1994	9	14	83.4	68.4 to 91.3
	1995	4	5	88.2	69.7 to 95.4
	1996	1	2	92.8	84.8 to 96.6
	1997	21	47	94.0	91.4 to 95.8
	1998	2	4	92.2	82.1 to 96.6
Northern Rivers	1993	2	7	97.3	94.1 to 98.8
	1994	12	39	98.3	97.3 to 98.9
	1995	7	26	97.9	96.5 to 98.7
	1996	3	9	97.4	92.3 to 99.1
	1997	5	19	98.1	96.6 to 98.9
	1998	2	4	90.8	67.1 to 97.5
Western Sydney	1993	3	9	94.0	88.1 to 97.0
	1994	5	9	88.7	78.3 to 94.1
	1995	8	8	79.9	56.4 to 90.8
	1996	8	14	91.6	83.9 to 95.6
	1997	20	32	87.7	81.0 to 92.0
	1998	5	6	80.4	52.0 to 92.0
Wentworth	1993	4	8	96.4	92.4 to 98.3
	1994	5	11	96.2	91.9 to 98.2
	1995	11	15	88.9	78.0 to 94.4
	1996	1	2	81.4	40.7 to 94.2
	1997	10	15	84.1	73.1 to 90.6
	1998	12	13	70.9	33.0 to 87.4
Southern & Greater Murray	1993	0	1	99.3	91.0 to 99.9
	1994	1	3	99.0	97.1 to 99.7
	1995	4	4	96.9	94.5 to 98.3
	1996	1	5	98.9	97.4 to 99.5
	1997	7	11	96.2	92.9 to 98.0
	1998	8	9	91.6	79.4 to 96.3

Table A6.1.3. VE estimates for children aged 5–8 years by health area,
1993–1998

Area	year	CV	n	VE (%)	95% CI (%)
Central & SE Sydney	1993	34	47	88.8	82.5 to 92.9
	1994	20	31	86.1	74.4 to 92.5
	1995	4	5	90.1	74.9 to 96.1
	1996	8	18	93.9	87.8 to 97.0
	1997	37	86	95.0	93.1 to 96.3
	1998	6	10	93.4	85.3 to 97.1
Northern Rivers	1993	5	15	97.8	95.1 to 99.0
	1994	15	90	98.5	97.8 to 99.0
	1995	11	67	98.2	97.2 to 98.9
	1996	2	10	97.8	93.5 to 99.2
	1997	7	56	98.4	97.2 to 99.0
	1998	1	3	92.3	72.5 to 97.9
Western Sydney	1993	11	21	95.0	90.3 to 97.4
	1994	22	32	90.5	82.6 to 94.8
	1995	20	24	83.2	64.6 to 92.0
	1996	11	19	93.0	86.8 to 96.3
	1997	45	63	89.7	84.8 to 93.0
	1998	9	12	83.6	60.6 to 93.2
Wentworth	1993	7	17	97.0	93.8 to 98.5
	1994	5	17	96.8	93.4 to 98.5
	1995	16	22	90.7	81.9 to 95.2
	1996	6	7	84.4	51.3 to 95.0
	1997	37	47	86.7	78.5 to 91.7
	1998	8	14	75.6	44.7 to 89.2
Southern & Greater Murray	1993	0	1	99.4	92.5 to 99.9
	1994	1	10	99.2	97.6 to 99.7
	1995	14	29	97.4	95.6 to 98.5
	1996	3	16	99.0	97.8 to 99.6
	1997	9	19	96.8	94.2 to 98.2
	1998	34	41	79.9	59.5 to 90.0

Table A6.1.4. VE estimates for children aged 9–13 years by health area, 1993–1998

Area	year	CV	n	VE (%)	95% CI (%)
Central & SE Sydney	1993	34	53	84.0	75.0 to 89.8
	1994	8	13	80.1	62.7 to 89.4
	1995	6	13	85.8	64.4 to 94.4
	1996	11	19	91.3	82.5 to 95.7
	1997	69	140	92.8	90.3 to 94.6
	1998	9	16	90.6	79.1 to 95.8
Northern Rivers	1993	5	18	96.8	93.1 to 98.5
	1994	10	69	97.9	96.8 to 98.6
	1995	16	54	97.4	95.9 to 98.4
	1996	0	3	96.8	90.7 to 98.9
	1997	9	34	97.7	96.0 to 98.6
	1998	2	4	89.0	60.7 to 96.9
Western Sydney	1993	10	17	92.8	86.1 to 96.3
	1994	10	14	86.4	74.6 to 92.7
	1995	15	22	75.9	49.0 to 88.6
	1996	14	18	89.9	81.0 to 94.6
	1997	59	83	85.2	78.3 to 89.9
	1998	12	15	76.5	43.6 to 90.2
Wentworth	1993	8	13	95.7	91.1 to 97.9
	1994	9	11	95.4	90.4 to 97.8
	1995	16	20	86.6	74.0 to 93.1
	1996	12	13	77.7	30.4 to 92.8
	1997	65	78	80.9	69.4 to 88.1
	1998	49	50	65.0	21.9 to 84.3
Southern & Greater Murray	1993	0	1	99.1	89.2 to 99.9
	1994	3	9	98.8	96.6 to 99.6
	1995	22	38	96.3	93.7 to 97.8
	1996	7	15	98.6	96.9 to 99.4
	1997	16	26	95.4	91.8 to 97.5
	1998	60	63	71.2	42.2 to 85.7

Appendix 6.2

Results of sensitivity analysis: VE estimates where 4 doses required in children aged over 18 months to be considered fully vaccinated, 1993–1998 notification data

Table A6.2.1. VE estimates for children aged 8–23 months by health area, 1993–1998

Area	year	CV	n	VE (%)	95% CI (%)
Central & SE Sydney	1993	1	3	87.8	77.3 to 93.4
	1994	6	6	85.1	68.7 to 92.9
	1995	2	3	88.7	68.8 to 95.9
	1996	1	4	94.7	87.4 to 97.8
	1997	4	13	94.7	91.1 to 96.8
	1998	0	3	93.0	82.4 to 97.2
Northern Rivers	1993	0	6	97.7	94.2 to 99.0
	1994	3	16	98.8	97.8 to 99.4
	1995	1	10	98.6	97.3 to 99.3
	1996	1	2	97.5	91.8 to 99.2
	1997	3	11	98.7	97.3 to 99.4
	1998	2	2	92.5	69.7 to 98.1
Western Sydney	1993	2	3	94.8	88.5 to 97.6
	1994	4	8	90.5	80.3 to 95.4
	1995	0	1	82.2	57.3 to 92.6
	1996	1	6	92.8	84.6 to 96.6
	1997	8	12	89.3	81.3 to 93.8
	1998	4	6	81.8	52.7 to 93.0
Wentworth	1993	0	4	96.7	92.5 to 98.6
	1994	0	1	96.8	92.4 to 98.7
	1995	1	4	90.0	78.2 to 95.4
	1996	1	3	85.1	49.2 to 95.6
	1997	7	10	86.0	74.0 to 92.5
	1998	0	1	74.1	34.3 to 89.8
Southern & Greater Murray	1993	1	3	99.3	91.3 to 99.9
	1994	1	2	99.4	97.7 to 99.8
	1995	0	6	98.3	96.4 to 99.2
	1996	0	3	99.2	97.9 to 99.7
	1997	4	8	96.8	93.4 to 98.4
	1998	2	3	79.5	53.0 to 91.0

Table A6.2.2. VE estimates for children aged 2–4 years by health area,
1993–1998

Area	year	CV	n	VE (%)	95% CI (%)
Central & SE Sydney	1993	9	18	79.9	66.3 to 88.0
	1994	8	13	75.6	52.1 to 87.5
	1995	4	5	81.5	51.1 to 93.0
	1996	1	2	91.3	80.2 to 96.2
	1997	18	44	91.3	87.2 to 94.1
	1998	2	4	88.5	72.5 to 95.2
Northern Rivers	1993	2	7	96.2	91.0 to 98.4
	1994	9	36	98.0	96.6 to 98.8
	1995	5	24	97.8	96.0 to 98.8
	1996	3	9	95.8	87.4 to 98.6
	1997	3	17	97.9	95.8 to 98.9
	1998	1	3	87.7	51.7 to 96.9
Western Sydney	1993	2	8	91.5	82.4 to 95.8
	1994	5	9	84.5	69.2 to 92.1
	1995	7	7	70.8	34.5 to 87
	1996	7	13	88.1	76.5 to 94
	1997	19	31	82.4	72.3 to 88.8
	1998	5	6	70.2	24.8 to 88.2
Wentworth	1993	4	8	94.6	88.4 to 97.5
	1994	4	10	94.8	88.5 to 97.7
	1995	10	14	83.7	66.9 to 92.0
	1996	1	2	75.6	18.6 to 92.7
	1997	9	14	77.0	60.3 to 86.7
	1998	11	12	57.6	-0.7 to 82.2
Southern & Greater Murray	1993	0	1	98.9	85.7 to 99.9
	1994	1	3	99.0	96.4 to 99.7
	1995	3	3	97.2	94.5 to 98.6
	1996	0	4	98.8	96.7 to 99.5
	1997	5	9	94.7	89.8 to 97.3
	1998	7	8	66.3	27.5 to 84.4

Table A6.2.3. VE estimates for children aged 5–8 years by health area, 1993–1998

Area	year	CV	n	VE (%)	95% CI (%)
Central & SE Sydney	1993	33	46	81.5	70.5 to 88.4
	1994	19	30	77.4	57.3 to 88.1
	1995	4	5	83.0	55.5 to 93.5
	1996	8	18	91.9	82.5 to 96.3
	1997	33	82	91.9	88.8 to 94.2
	1998	6	10	89.3	75.3 to 95.4
Northern Rivers	1993	5	15	96.5	91.9 to 98.4
	1994	11	86	98.2	97.0 to 98.9
	1995	8	64	98.0	96.5 to 98.8
	1996	2	10	96.2	88.4 to 98.7
	1997	6	55	98.0	96.3 to 98.9
	1998	1	3	88.7	55.8 to 97.1
Western Sydney	1993	10	20	92.1	84.3 to 96.0
	1994	19	29	85.7	72.8 to 92.4
	1995	20	24	73.1	41.8 to 87.5
	1996	10	18	89.1	78.8 to 94.3
	1997	43	61	83.7	75.7 to 89.1
	1998	9	12	72.5	32.2 to 88.8
Wentworth	1993	7	17	95.0	89.6 to 97.6
	1994	5	17	95.2	89.6 to 97.8
	1995	16	22	84.9	70.2 to 92.4
	1996	6	7	77.5	26.6 to 93.1
	1997	36	46	78.8	65.2 to 87.1
	1998	8	14	60.9	8.8 to 83.2
Southern & Greater Murray	1993	0	1	99.0	86.9 to 99.9
	1994	0	9	99.1	96.7 to 99.8
	1995	7	22	97.4	95.1 to 98.6
	1996	2	15	98.8	97.0 to 99.6
	1997	9	19	95.1	90.9 to 97.4
	1998	33	40	68.9	35.8 to 84.9

Table A6.2.4. VE estimates for children aged 9–13 years by health area, 1993–1998

Area	year	CV	n	VE (%)	95% CI (%)
Central & SE Sydney	1993	33	52	74.7	59.8 to 84.1
	1994	8	13	69.2	40.9 to 84.0
	1995	6	13	76.8	40.0 to 91.0
	1996	6	14	89.0	76.0 to 95.0
	1997	66	137	89.0	85.1 to 91.9
	1998	8	15	85.5	66.6 to 93.7
Northern Rivers	1993	4	17	95.2	89.0 to 97.9
	1994	6	65	97.5	96.0 to 98.5
	1995	9	47	97.2	95.2 to 98.4
	1996	0	3	94.8	84.1 to 98.3
	1997	5	30	97.3	94.9 to 98.6
	1998	2	4	84.5	39.9 to 96
Western Sydney	1993	10	17	89.2	78.6 to 94.6
	1994	9	13	80.4	62.3 to 89.8
	1995	15	22	63.3	20.2 to 83.1
	1996	13	17	85.1	71.0 to 92.3
	1997	51	75	77.8	67.0 to 85.1
	1998	12	15	62.5	7.6 to 84.8
Wentworth	1993	8	13	93.2	85.8 to 96.8
	1994	8	10	93.5	85.8 to 97.0
	1995	16	20	79.5	59.2 to 89.7
	1996	11	12	69.3	0.3 to 90.6
	1997	63	76	71.1	53.0 to 82.3
	1998	47	48	46.7	-22.4 to 76.8
Southern & Greater Murray	1993	0	1	98.6	82.1 to 99.9
	1994	2	8	98.8	95.5 to 99.7
	1995	14	30	96.5	93.4 to 98.1
	1996	6	14	98.4	96.0 to 99.4
	1997	15	25	93.4	87.7 to 96.4
	1998	54	57	57.6	12.8 to 79.4

Appendix 6.3

Results of sensitivity analysis: VE estimates where partially vaccinated classified as unvaccinated, 1993-1998 notification data

Table A6.3.1. VE estimates for children aged 8–23 months by health area, 1993–1998

Area	year	CV	n	VE (%)	95% CI (%)
Central & SE Sydney	1993	1	4	81.2	67.4 to 89.1
	1994	6	7	77.3	56.4 to 88.2
	1995	2	3	80.6	50.8 to 92.4
	1996	1	4	92.4	83.4 to 96.5
	1997	4	16	91.3	86.2 to 94.5
	1998	0	3	89.0	74.6 to 95.2
Northern Rivers	1993	0	7	96.1	91.0 to 98.3
	1994	3	16	97.8	96.1 to 98.8
	1995	1	10	97.7	95.7 to 98.8
	1996	1	4	95.8	87.7 to 98.6
	1997	3	11	97.6	95.2 to 98.8
	1998	2	2	87.1	54.0 to 96.4
Western Sydney	1993	2	4	89.5	78.5 to 94.8
	1994	4	9	82.1	65.6 to 90.7
	1995	0	2	68.7	33.8 to 85.2
	1996	1	6	88.3	77.4 to 93.9
	1997	8	12	81.8	70.3 to 88.8
	1998	4	6	57.6	-3.7 to 82.7
Wentworth	1993	0	4	92.6	84.1 to 96.6
	1994	0	1	93.5	85.6 to 97.1
	1995	1	5	83.3	67.5 to 91.5
	1996	1	4	80.4	49.4 to 92.4
	1997	7	12	75.6	58.3 to 85.7
	1998	0	1	60.9	16.8 to 81.6
Southern & Greater Murray	1993	1	3	97.9	76.8 to 99.8
	1994	1	2	98.4	94.5 to 99.5
	1995	0	6	96.5	93.2 to 98.2
	1996	0	5	98.2	95.5 to 99.3
	1997	4	8	92.9	86.6 to 96.2
	1998	2	4	75.6	55.8 to 86.5

Table A6.3.2. VE estimates for children aged 2–4 years by health area, 1993–1998

Area	year	CV	n	VE (%)	95% CI (%)
Central & SE Sydney	1993	9	20	70.3	53.2 to 81.2
	1994	8	15	64.3	35.5 to 80.2
	1995	4	5	69.4	25.6 to 87.5
	1996	1	2	88.0	74.9 to 94.3
	1997	18	47	86.3	80.5 to 90.3
	1998	2	4	82.6	61.8 to 92.1
Northern Rivers	1993	2	8	93.8	86.5 to 97.2
	1994	9	39	96.5	94.3 to 97.9
	1995	5	29	96.4	93.8 to 97.9
	1996	3	9	93.4	81.5 to 97.6
	1997	3	20	96.2	93.0 to 98.0
	1998	1	4	79.7	29.8 to 94.1
Western Sydney	1993	2	9	83.4	68.1 to 91.3
	1994	5	9	71.7	48.2 to 84.6
	1995	7	9	50.6	2.1 to 75.1
	1996	7	15	81.5	66.8 to 89.8
	1997	19	32	71.3	57.5 to 80.6
	1998	5	6	33.2	-59.2 to 72.0
Wentworth	1993	4	9	88.3	76.3 to 94.3
	1994	4	11	89.8	78.9 to 95.0
	1995	10	17	73.7	52.3 to 85.5
	1996	1	4	69.2	22.5 to 87.7
	1997	9	15	61.5	38.6 to 75.9
	1998	11	13	38.4	-22.3 to 68.9
Southern & Greater Murray	1993	0	1	96.8	63.4 to 99.7
	1994	1	4	97.5	91.6 to 99.3
	1995	3	4	94.5	90.0 to 97.0
	1996	0	6	97.2	93.1 to 98.8
	1997	5	11	88.8	80.2 to 93.7
	1998	7	9	61.5	35.2 to 77.1

Table A6.3.3. VE estimates for children aged 5–8 years by health area, 1993–1998

Area	year	CV	n	VE (%)	95% CI (%)
Central & SE Sydney	1993	33	52	71.2	56.6 to 80.9
	1994	19	32	65.4	39.2 to 80.3
	1995	4	6	70.4	28.8 to 87.7
	1996	8	19	88.4	76.6 to 94.2
	1997	33	90	86.7	82.1 to 90.1
	1998	6	11	83.1	63.9 to 92.1
Northern Rivers	1993	5	18	94.0	87.2 to 97.2
	1994	11	93	96.6	94.7 to 97.9
	1995	8	70	96.5	94.2 to 97.9
	1996	2	10	93.6	82.2 to 97.7
	1997	6	56	96.3	93.4 to 98
	1998	1	3	80.3	32.2 to 94.3
Western Sydney	1993	10	22	83.9	70.0 to 91.4
	1994	19	32	72.6	51.7 to 84.5
	1995	20	24	52.1	7.8 to 75.1
	1996	10	24	82.1	68.5 to 89.8
	1997	43	68	72.2	60.7 to 80.3
	1998	9	12	35.2	-51.4 to 72.3
Wentworth	1993	7	17	88.7	77.5 to 94.3
	1994	5	18	90.1	79.9 to 95.1
	1995	16	24	74.5	54.7 to 85.7
	1996	6	7	70.1	26.2 to 87.9
	1997	36	51	62.7	43.2 to 75.5
	1998	8	14	40.2	-16.5 to 69.3
Southern & Greater Murray	1993	0	1	96.8	64.6 to 99.7
	1994	0	10	97.6	92.0 to 99.3
	1995	7	30	94.6	90.7 to 96.9
	1996	2	16	97.3	93.5 to 98.8
	1997	9	25	89.1	81.4 to 93.6
	1998	33	45	62.6	40.1 to 76.7

Table A6.3.4. VE estimates for children aged 9–13 years by health area, 1993–1998

Area	year	CV	n	VE (%)	95% CI (%)
Central & SE Sydney	1993	33	53	62.1	42.7 to 74.9
	1994	8	13	54.3	18.8 to 74.3
	1995	6	13	60.9	6.9 to 83.6
	1996	6	19	84.7	69.2 to 92.4
	1997	66	147	82.4	76.8 to 86.7
	1998	8	17	77.7	52.7 to 89.5
Northern Rivers	1993	4	19	92.1	83.2 to 96.3
	1994	6	70	95.5	93.0 to 97.2
	1995	9	57	95.4	92.3 to 97.2
	1996	0	5	91.5	76.5 to 97.0
	1997	5	34	95.2	91.3 to 97.3
	1998	2	4	74.0	10.8 to 92.4
Western Sydney	1993	10	17	78.8	60.3 to 88.6
	1994	9	14	63.9	35.4 to 79.8
	1995	15	23	36.8	-21.9 to 67.3
	1996	13	19	76.4	58.3 to 86.6
	1997	51	88	63.3	48.5 to 73.9
	1998	12	15	14.6	-99.3 to 63.4
Wentworth	1993	8	13	85.1	70.3 to 92.5
	1994	8	11	86.9	73.4 to 93.6
	1995	16	21	66.4	40.1 to 81.2
	1996	11	13	60.6	3.2 to 84.0
	1997	63	79	50.8	25.8 to 67.4
	1998	47	52	21.2	-50.9 to 58.8
Southern & Greater Murray	1993	0	1	95.8	53.4 to 99.6
	1994	2	9	96.8	89.4 to 99.0
	1995	14	39	92.9	87.8 to 95.9
	1996	6	18	96.4	91.4 to 98.5
	1997	15	28	85.7	75.5 to 91.6
	1998	54	69	50.8	21.6 to 69.1

Table A6.3.5. VE estimates by age and year, adjusted for health area, 1993–1998

Age group and year	CV	n	VE (%)	95% CI (%)
8–23 months				
1993	4	22	93.4	83.8 to 97.3
1994	14	35	93.7	88.7 to 96.5
1995	4	26	90.2	84.3 to 93.9
1996	4	23	93.2	88.4 to 96.0
1997	26	59	90.6	80.7 to 95.4
1998	8	16	77.1	61.7 to 86.3
2–4 years				
1993	17	47	89.5	75.1 to 95.6
1994	27	78	90.0	83.6 to 94.0
1995	29	64	84.6	77.6 to 89.4
1996	12	36	89.3	83.1 to 93.2
1997	54	125	85.2	71.3 to 92.4
1998	26	36	63.9	44.3 to 76.6
5–8 years				
1993	55	110	86.6	76.3 to 95.6
1994	54	185	87.3	84.6 to 93.9
1995	55	154	80.3	79.3 to 89.2
1996	28	76	86.3	84.1 to 93.2
1997	127	290	81.1	72.9 to 92.4
1998	57	85	53.8	47.9 to 76.4
9–13 years				
1993	55	103	86.60	68.8 to 94.3
1994	33	117	87.27	79.6 to 92.1
1995	60	153	80.31	72.9 to 85.7
1996	36	74	86.33	79.2 to 91.0
1997	200	376	81.10	75.4 to 85.5
1998	123	157	53.82	32.2 to 68.6

Table A6.3.6. VE estimates by age and health area, adjusted for year, 1993–1998

Age group and year	CV	n	VE (%)	95% CI (%)
8–23 months				
Central & SE Sydney	14	37	86.5	78.9 to 91.3
Western Sydney	19	39	84.3	70.0 to 87.4
Wentworth	9	27	80.6	69.9 to 91.8
Northern Rivers	10	50	96.3	94.0 to 97.7
Southern & Greater Murray	8	28	96.1	92.9 to 97.9
2–4 years				
Central & SE Sydney	42	93	78.7	70.0 to 84.9
Western Sydney	45	80	75.3	57.2 to 78.1
Wentworth	39	69	69.4	56.0 to 86.1
Northern Rivers	23	109	94.2	91.4 to 96.1
Southern & Greater Murray	16	35	93.8	89.3 to 96.4
5–8 years				
Central & SE Sydney	103	210	79.4	72.5 to 84.5
Western Sydney	111	182	76.0	60.8 to 77.5
Wentworth	78	131	70.3	58.4 to 86.2
Northern Rivers	33	250	94.3	91.9 to 96.0
Southern & Greater Murray	51	127	94.0	90.0 to 96.4
9–13 years				
Central & SE Sydney	127	262	72.8	64.0 to 79.4
Western Sydney	110	176	60.9	48.1 to 70.5
Wentworth	153	189	92.5	57.4 to 76.5
Northern Rivers	26	189	72.8	89.4 to 94.8
Southern & Greater Murray	91	164	68.4	86.9 to 95.3

Appendix 6.4

VE estimates where cases are required to be laboratory confirmed, 1993-1998 notification data

Table A6.4.1. VE estimates for children aged 8–23 months by health area, 1993–1998

Area	year	CV	n	VE (%)	95% CI (%)
Central & SE Sydney	1993	0	0	-	-
	1994	0	0	-	-
	1995	1	2	95.1	83.3 to 98.6
	1996	1	4	96.0	90.0 to 98.4
	1997	1	5	96.9	94.2 to 98.3
	1998	0	1	95.4	85.8 to 98.5
Northern Rivers	1993	0	1	98.3	95.1 to 99.4
	1994	1	10	99.2	98.3 to 99.6
	1995	0	4	98.7	97.3 to 99.4
	1996	1	1	98.5	94.2 to 99.6
	1997	0	4	99.5	98.6 to 99.8
	1998	2	2	91.8	64.1 to 98.1
Western Sydney	1993	1	1	96.5	91.4 to 98.6
	1994	3	6	94.3	86.7 to 97.5
	1995	1	2	89.7	74.3 to 95.8
	1996	0	3	92.7	82.3 to 97.0
	1997	5	8	92.1	84.9 to 95.8
	1998	2	4	90.5	75.0 to 96.4
Wentworth	1993	0	3	98.0	95.0 to 99.2
	1994	0	1	97.3	93.5 to 98.9
	1995	1	3	93.0	83.4 to 97.1
	1996	1	3	91.6	72.1 to 97.5
	1997	6	8	89.8	79.5 to 94.9
	1998	0	0	-	-
Southern & Greater Murray	1993	0	2	100.0	100 to 100
	1994	0	1	98.8	95.2 to 99.7
	1995	0	4	98.2	96.0 to 99.2
	1996	0	2	99.1	97.7 to 99.7
	1997	2	5	98.0	95.7 to 99.1
	1998	1	2	86.8	69.2 to 94.3

Table A6.4.2. VE estimates for children aged 2–4 years by health area, 1993–1998

Area	year	CV	n	VE (%)	95% CI (%)
Central & SE Sydney	1993	4	8	81.5	64.0 to 90.5
	1994	2	3	76.8	41.8 to 90.8
	1995	0	0	-	-
	1996	0	1	90.9	78.7 to 96.1
	1997	9	24	92.9	89.0 to 95.5
	1998	0	1	89.5	69.8 to 96.3
Northern Rivers	1993	1	5	96.1	90.0 to 98.5
	1994	7	29	98.1	96.8 to 98.9
	1995	4	20	97.0	94.8 to 98.3
	1996	1	5	96.5	87.8 to 99.0
	1997	1	5	98.8	97.0 to 99.5
	1998	1	3	81.3	21.3 to 95.6
Western Sydney	1993	1	6	92.1	82.6 to 96.4
	1994	2	5	86.9	71.7 to 93.9
	1995	6	6	76.4	47.0 to 89.5
	1996	6	7	83.3	63.5 to 92.4
	1997	13	21	81.9	70.3 to 89.0
	1998	3	4	78.3	46.2 to 91.3
Wentworth	1993	3	7	95.4	89.9 to 97.9
	1994	5	11	93.9	87.1 to 97.1
	1995	4	8	84.0	65.9 to 92.5
	1996	1	2	80.9	38.5 to 94.0
	1997	7	9	76.7	58.0 to 87.1
	1998	8	9	67.1	21.9 to 86.1
Southern & Greater Murray	1993	0	1	100.0	100 to 100
	1994	1	1	97.2	89.7 to 99.3
	1995	2	2	95.9	91.7 to 98.0
	1996	1	4	98.0	95.2 to 99.2
	1997	5	9	95.5	91.2 to 97.7
	1998	8	9	69.8	37.2 to 85.4

Table A6.4.3. VE estimates for children aged 5–8 years by health area, 1993–1998

Area	year	CV	n	VE (%)	95% CI (%)
Central & SE Sydney	1993	16	21	81.5	65.8 to 89.9
	1994	12	17	76.8	44.7 to 90.3
	1995	2	3	88.9	64.8 to 96.5
	1996	4	11	90.9	79.8 to 95.9
	1997	18	58	92.9	89.8 to 95.1
	1998	4	6	89.4	71.0 to 96.2
Northern Rivers	1993	4	9	96.1	90.3 to 98.5
	1994	11	78	98.1	97.0 to 98.8
	1995	9	48	97.0	95.1 to 98.2
	1996	2	8	96.5	87.9 to 99.0
	1997	1	36	98.8	97.2 to 99.5
	1998	1	2	81.3	21.7 to 95.5
Western Sydney	1993	8	15	92.1	83.3 to 96.2
	1994	12	18	86.9	73.0 to 93.6
	1995	15	19	76.4	49.4 to 89.0
	1996	9	14	83.3	64.8 to 92.1
	1997	36	49	81.9	72.3 to 88.1
	1998	8	11	78.3	48.2 to 90.9
Wentworth	1993	5	13	95.4	90.2 to 97.8
	1994	5	14	93.9	87.4 to 97.1
	1995	15	18	84.0	67.2 to 92.2
	1996	4	5	80.8	40.1 to 93.9
	1997	33	40	76.7	60.8 to 86.1
	1998	5	11	67.0	23.9 to 85.7
Southern & Greater Murray	1993	0	1	100.0	100 to 100
	1994	1	5	97.2	90.0 to 99.2
	1995	9	17	95.9	92.2 to 97.9
	1996	2	13	98.0	95.4 to 99.2
	1997	6	13	95.5	91.5 to 97.6
	1998	33	40	69.7	40.6 to 84.5

Table A6.4.4. VE estimates for children aged 9–13 years by health area, 1993–1998

Area	year	CV	n	VE (%)	95% CI (%)
Central & SE Sydney	1993	19	30	70.3	45.4 to 83.8
	1994	6	9	62.8	10.0 to 84.6
	1995	5	10	82.2	44.4 to 94.3
	1996	10	16	85.3	67.9 to 93.3
	1997	55	106	88.7	84.2 to 91.9
	1998	6	11	83.1	53.9 to 93.8
Northern Rivers	1993	3	13	93.8	84.5 to 97.5
	1994	10	67	96.9	95.2 to 98.1
	1995	15	49	95.2	92.2 to 97.0
	1996	0	3	94.4	80.5 to 98.4
	1997	6	28	98.0	95.5 to 99.1
	1998	2	3	70.0	-25.3 to 92.8
Western Sydney	1993	8	13	87.3	73.2 to 94.0
	1994	7	11	79.0	56.3 to 89.9
	1995	12	18	62.1	18.4 to 82.4
	1996	13	17	73.2	43.6 to 87.3
	1997	51	70	70.9	55.9 to 80.9
	1998	11	14	65.2	17.0 to 85.4
Wentworth	1993	8	13	92.5	84.3 to 96.5
	1994	9	11	90.2	79.7 to 95.3
	1995	16	20	74.4	47.4 to 87.5
	1996	10	11	69.2	4.6 to 90.1
	1997	56	69	62.6	37.7 to 77.5
	1998	42	43	47.1	-19.8 to 76.7
Southern & Greater Murray	1993	0	1	100.0	100 to 100
	1994	3	5	95.5	84.0 to 98.8
	1995	14	25	93.5	87.6 to 96.6
	1996	7	11	96.9	92.7 to 98.7
	1997	15	25	92.7	86.5 to 96.1
	1998	58	61	51.4	5.0 to 75.2

Chapter 7

Summary and recommendations

Although mortality and morbidity from pertussis declined dramatically following the introduction of mass vaccination programs in 1953, this thesis demonstrates that pertussis remains an important public health problem in Australia. The 1997 pertussis epidemic, which affected a large proportion of Australia, resulted in six infant deaths, over 1000 hospitalisations and almost 11 000 notifications. During the period 1993 to 1998, more children were hospitalised with pertussis than with any other vaccine preventable disease and pertussis had the highest notification rate, both in children and overall.[1]

The data presented in this thesis confirm that, despite the high notification rates for pertussis in the 1990s in Australia, notifications considerably underestimate the true incidence. Estimating the incidence of pertussis in any given geographical area and time period is difficult. Moreover, under-notification may not remain constant over time and between areas. The extent of under-notification among infants is highlighted in Chapters 2 & 3 in the comparison of notifications and hospitalisations. The extent of under-notification in adolescents and adults is likely to be even greater than in younger age groups. The implementation of laboratory notification and the widespread use of a commercially available serological kit by diagnostic laboratories in the early 1990s has resulted in notification of a much higher proportion of cases in older children than in comparable industrialised countries. However, data presented in this thesis show that notification rates in adolescents have continued to increase, despite the proportion of serologically diagnosed cases remaining constant since 1994.

Notification and hospitalisation data are currently under-utilised in Australia. This thesis has highlighted their usefulness in monitoring disease incidence. Despite the limitations of routine data collections, these data provide valuable information about the epidemiology of pertussis and the impact of vaccination programs. In view of the continued burden of disease from pertussis and the changes in vaccination policy in Australia it will be important to continue and improve surveillance and to make better use of the data collected. Improvements include the incorporation into the national database of data available at a State/Territory level, such as date of birth, method of diagnosis and vaccination status. Additional research projects could be undertaken to determine the validity of various aspects of the notification and hospitalisation data.

Hospitalisation data in particular are under-utilised. This thesis demonstrates the value of hospitalisation data in examining variations in reporting practices, and suggests that hospitalisation data may be more useful for monitoring trends and making interstate and international comparisons in infant pertussis than notification data.

The case definition for pertussis notification in Australia is currently under review, yet we have no idea to what extent notified cases meet the current case definition or whether this varies between the States and Territories. Problems with the available method of diagnosis data in NSW were identified in Chapter 3 — validation of these data would be useful and could result in improved recording. Two studies undertaken in NSW have examined the notifying practices of general practitioners,[2,3] but no studies have examined the notifying practices of hospital doctors. Anecdotal evidence suggests that doctors in hospitals are less likely to notify, as it is less clear whose responsibility it is to notify the local public health unit. Such validation studies would assist the interpretation of routinely collected data.

Although complete vaccination of all children is the most important preventive measure in maintaining control of pertussis,[4] prior to this thesis, no published data on the effectiveness of pertussis vaccines used in Australia were available. Since 1993 there have been significant changes in the Australian standard vaccination schedule with respect to pertussis control. In 1994, a fifth dose of DTP for children aged 4–5 years was added to the schedule. The impact of this additional booster dose on notifications in the 5–9year age group is evident from the detailed age-specific data presented in Chapters 2 & 3. The 5-9 year age group now has lower notification rates, compared with historical data and relative to 10–14 year olds, whose notification rates currently exceed those of any other age group, including infants.

In children aged less than two years there is an association between eligibility for vaccination and notification/hospitalisation rates (Chapter 3). The decrease in notification and hospitalisation rates strongly suggests an effect of vaccination. The analyses which demonstrated this would not have been possible without information on the date of birth and/or the age in months at disease onset. In the future, as the national data collection improves, these analyses should be repeatable at a national level and should become part of routine notification reports.

The other important change in the Australian vaccination schedule was the licensing of acellular pertussis vaccines in 1997. It was hoped that these vaccines, which have fewer side effects than whole-cell vaccines, would result in improved uptake of pertussis vaccine. Coverage at 12 and 24 months of age, as recorded on the ACIR, has improved since acellular vaccines were licensed but the contribution of acellular vaccines to this improved coverage cannot be distinguished from that of other program initiatives using the available data. Since 1999, acellular vaccines have been funded nationally for all doses. The ability to track changes in vaccine type over time at a national level, as shown in Chapter 4, would not have been possible before the ACIR was established. In the year 2000, the ACIR recorded use of only a very small proportion of whole-cell pertussis vaccines (Chapter 4). It will be important to monitor trends in pertussis hospitalisation and notification rates among infants, using methods similar to those described in this thesis, to evaluate the combined impact of pertussis vaccine coverage and acellular vaccine effectiveness in this target group.

The importance of monitoring the vaccine effectiveness of routinely used, publicly funded vaccines was highlighted by the presentation in Chapter 6 of previously unavailable VE estimates for pertussis in New South Wales. VE estimations should be incorporated into routine analyses of notification data using coverage data from the ACIR. The impact of the introduction of the fifth dose on pertussis notification rates in 10–14 year olds will need to be closely monitored. Uptake of the new booster dose for adolescents and adults also needs to be monitored to determine its effect. The ACIR records only vaccines given to children below the age of seven years, so alternative methods of measuring vaccine uptake will need to be used for adolescents and adults.

More important than the individual pertussis vaccine effectiveness figures presented in this thesis is the process involved in their calculation. The methodology developed in Chapter 6 for the routine monitoring of pertussis vaccine effectiveness, involved linkage of previously isolated data sets (pertussis notification data and ACIR data). This has the potential to be incorporated into routine evaluation of other diseases for which vaccines are available. One of the main drawbacks of the VE study presented here was difficulty in determining whether the measured differences in VE (between

areas and over time) were real or attributable to inaccuracies in vaccine coverage data. In the future, as the ACIR matures, this will be less of a problem, as it will be possible to use population coverage data of the cohort of children from which the cases arose, thus improving the precision of the VE estimates. In addition, checking the immunisation status of cases will be easier and the population estimates will be more accurate.

In spite of high levels of vaccination amongst infants, pertussis continues to challenge Australian public health authorities. Factors responsible for difficulties in pertussis control include the limited duration of protection, problems associated with diagnosis of pertussis, especially in older or vaccinated persons and during the early most infectious phase. The data presented in this thesis can be used as a baseline for the assessment of future strategies aimed at pertussis control.

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Appendix 1

Study proposal for a survey of cough and pertussis immunisation status in children

This appendix contains an application to the Ethics Committee of the Children's Hospital at Westmead. I was responsible for writing most of this study proposal but not the parts which address aims 4 & 5 (the utility of clinical symptoms as a screening tool for pertussis and validating the test properties of symptomatology as a screening tool against serology). The analyses of some of the data resulting from this study form the major part of another student's masters thesis.

Short Title of Project:

Survey of cough and pertussis immunisation status in children

Investigators:

1. Dr Raina MacIntyre MAppEpid, PhD, FRACP, FAFPHM, Senior lecturer. Email address: RainaM@chw.edu.au

2. A/Prof Peter McIntyre PhD FRACP FAFPHM, Deputy Director. Email address: Peterm@chw.edu.au

3. Ms Michelle Cagney BSc – Third year Graduate Medical Program student of University of Sydney, undertaking an MPH program in 2000. Email address: MichelC5@chw.edu.au

4. Ms Siranda Torvaldsen GradDipHSci(Epi&Stats), MAppEpid, Research Officer/PhD Candidate. Email address: SirandaT@chw.edu.au

National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases

The Children's Hospital at Westmead

Telephone: (02) 9845 0520

Facsimile: (02) 9845 3082

SCIENTIFIC PROTOCOL

Aims

1. To estimate the incidence of pertussis in New South Wales children aged 5–14 years.

2. To determine vaccination coverage in children aged 5–14 years.

3. To estimate the effectiveness of pertussis vaccination.

4. To assess the utility of clinical symptoms as a screening tool for pertussis.

5. To validate the test properties of symptomatology as a screening tool against serology.

Simple description

Whooping cough (pertussis) is epidemic in Australia, with an increasing proportion of cases in older children and adolescents. The study has two parts:

1. A cross-sectional telephone survey will be conducted to determine cough symptomatology, history of respiratory illness, vaccination history and risk factors in 2000 children aged 5–14 years in Western Sydney Area Health Service (WSAHS). All children will be invited to participate in the second part of the study.

2. A cross-sectional serosurvey will be conducted to determine exposure to pertussis in 200 consenting subjects from part (1).

Background

Pertussis in NSW

In terms of morbidity and mortality, pertussis is the most important vaccine preventable disease in Australia. Pertussis has been epidemic in Australia since 1993[1] and has been responsible for six infant deaths in New South Wales since late 1996. Immunisation has changed the epidemiology of pertussis, with an increasing proportion of cases now seen in older children, adolescents and adults. These populations may then transmit pertussis to neonates and infants who are most vulnerable.

Symptoms as a screening tool

Attempts have been made to develop clinical definitions of pertussis based on the associated symptoms. An American study by Wright et al[2] (1995) found that 21% of people ≥18 years presenting to the emergency room of an urban university hospital had evidence of pertussis infection. Similar results were reported by Schmitt-Gohe et al[3] (1995) who also found a weak association with the presence of a whoop (38% of subjects, 24/64). A Sydney-based study[4] examining the spectrum of symptoms in adults with notified pertussis aged ≥20 years found that 82% (60/73) experienced paroxysms, 66% (48/73) an inspiratory whoop and 62% (47/73) reported post-tussive vomiting.

Whilst various clinical case definitions exist, there is no universal consensus as to which definition should be accepted. It has been well documented that the sensitivity of laboratory-based diagnostic tools decreases in an individual with a history of pertussis immunisation.[5] To this end, a more sensitive clinical diagnosis may help to diagnose and treat adolescent and adult cases of pertussis which, although endemic, are under-diagnosed.

Vaccine effectiveness

Vaccine effectiveness (VE) studies become particularly important when disease incidence does not predictably decrease with increased vaccine coverage, when high proportions of fully immunised cases are reported or when issues arise that were not predicted in pre-licensure evaluations.[6] At present one of the investigators of this proposed study is also undertaking a study which aims to estimate VE in New South Wales children using the screening method. The screening method estimates VE by comparing the proportion of persons with the disease who are vaccinated with the proportion of the population who are vaccinated.[7-10]

Justification for this study

The study will enable us to determine the rate of pertussis disease and vaccination coverage in older children and adolescents, and to evaluate the sensitivity of various clinical algorithms in the diagnosis of pertussis. Symptomatology may be an important screening tool in the adolescent and adult populations, where pertussis is poorly diagnosed.

Using vaccine coverage information, VE estimates could be calculated and compared with estimates using notified cases. The study will provide information on the effect of case ascertainment bias and help predict true VE figures. There was a change to the standard immunisation schedule in 1994 with the introduction of a 5th dose for 4-5 year olds. Some of the study subjects will have been eligible for this dose, thus allowing its effectiveness to be evaluated.

Methods

Subjects

Children aged 5–14 years living in the general community in WSAHS. The first part of the study will involve a telephone survey of 2000 such children. In the second part of the study, 10% of subjects will be tested for pertussis by serology. This will comprise of 50 (cough) and 150 controls (no cough).

Recruitment of subjects and controls

Two thousand households with at least one child aged 5–14 years of age will be selected from WSAHS. Where a household has more than one child of eligible age, the child with the birth date closest to the interview date will be selected. Consenting parents or guardians will be interviewed using a structured questionnaire (attached). Two hundred subjects (50 cases with cough and 150 controls without cough) will be selected for serological testing. If >200 subjects consent, 50 cases and 150 age-matched controls will be randomly selected. A nurse experienced in venesection will do home visits, will provide a plain language statement, obtain consent and collect blood. Written, informed consent will be sought from the parent/guardian. However, if the child refuses, venesection will not be performed.

Power analysis and sample size

Sample size was calculated to detect a prevalence of cough of 5% with a 95% confidence interval and 80% power. Allowing for a refusal rate of 20%, 2000 households in WSAHS with at least one child aged 5–14 years of age will be randomly selected from the White Pages for the telephone survey.

Measuring instruments:

A. Questionnaire & interview

The telephone survey will be conducted using computer assisted telephone interviews (CATI). These will be undertaken by the NCS Australasia Ply Ltd. A pilot survey will be conducted prior to the commencement of the study.

Outcome variables measurement

The questionnaire will determine risk factors for cough, a history of ever having had a cough lasting 2 weeks or longer, and whether the coughing illness was in the previous 12 months and associated with any other symptoms such as a 'whoop' or post-tussive vomiting. Respiratory disease history and DTP immunisation history will also be sought.

Validation of symptomatology

The symptoms reported by study subjects will be validated using pertussis serology from children who reported a cough history suggestive of pertussis and from those who did not report cough. Various symptom clusters will be analysed against results of serology to determine the most sensitive method of diagnosing pertussis clinically.

B. Laboratory methods

An 'in house' enzyme linked immunosorbent assay (ELISA) will be used to measure antibodies (IgG) to pertussis antigens (pertussis toxin and filamentous haemagglutinin) at the serology laboratory of the Children's Hospital at Westmead.

Analysis of data

Rates of cough

The following rates in children aged 5–14 years will be calculated:

1. Cough lasting 2 or more weeks
2. Cough lasting 3 or more weeks
3. Cough lasting 2 or more weeks with one other symptom
4. Cough lasting 3 or more weeks with one other symptom
5. Doctor-diagnosed pertussis
6. Age-specific rates of all the above.

Immunisation status

The proportion of subjects fully immunised, partially immunised and unimmunised will be calculated. Also, the proportion of children whose parents can verify the immunisation status by referring to the dates in a written record will be calculated. These proportions will also be calculated by age group.

Vaccine effectiveness (VE)

VE will be estimated by age group by the formula VE = 1-[PCV/(1-PCV) x 1-PPV/PPV], where PCV is the proportion of the vaccinated population with the disease and PPV is the proportion of the population vaccinated.

Validation of symptoms against serology

Symptom clusters will be analysed in cases and controls to determine their test characteristics as a screening tool for pertussis using 2 x 2 tables for diagnostic tests, and by using serology and clinical history of pertussis, alternatively, as the gold standard.

The data collected will be analysed by the statistical software "EpiInfo version 6.04" and SAS. Statistical significance will be defined as a p-value of 0.05 or less.

Interpretation and application of results

The effect of applying different case definitions will be examined. The utility of symptoms as a screening tool for pertussis in older children will be evaluated. Some of the results of this study will be included in Michelle Cagney's masters thesis. The study results will also be submitted for publication in a peer-reviewed journal.

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ETHICAL ANALYSIS

Potential risks

This study poses no risk for participants of the telephone survey. A blood sample will be taken from those respondents who agree to the serology test. The disadvantage of performing venesection is the possibility of minor pain and possible bruising at the needle site. The rate at which these side effects occur is operator dependent but they occur at a low frequency. EMLA patches will be provided.

Potential benefits

Successful completion of this research topic will provide a number of benefits. Firstly, it would provide an estimate of the prevalence of pertussis and vaccine coverage among children aged 5–14 years in NSW. Secondly, a sensitive and specific clinical

definition of pertussis will allow the doctor to order the appropriate laboratory-based tests earlier in the disease than at present, increasing the chance of obtaining a true-positive result. It would also make it possible to estimate the effectiveness of the current vaccine schedule, with recommendations being made to the appropriate governing bodies on the introduction of an adolescent booster dose of the pertussis vaccine.

Research plan

Proposed date of commencement

The proposed commencement date for the interviews is at the end of June and throughout July 2000 (after peak pertussis activity has ceased).

Estimated duration

It is estimated that the serology samples will be collected by August, with analysis and data cleaning occurring in November. A report is to be prepared by the end of December 2000.

Budget

CATI survey (by NCS, including pilot, including GST)	$ 74,800
Serology (reagents only, including GST)	$ 8,800
Nurses for venesection	$ 20,000
Laboratory staff time	$ 10,000
Telephone, stationary, miscellaneous	$ 2,000
TOTAL	$155,600

Source of funds

The project is being funded by SmithKline Beecham Biologicals, whom we approached for funding. It is an investigator-driven study and SmithKline Beecham has had no input into the study aims, design or execution, and will not have any such input.

Staffing

Telephone surveys will be conducted by experienced staff at NCS Australasia Pty Ltd, a market research company selected by competitive tender. Blood samples will be obtained by the clinical nurses working for the NCIRS, whilst serology will be

performed by the microbiology department at the Children's Hospital at Westmead. Analysis will be conducted by Michelle Cagney, a student at the NCIRS.

Care of participants

This study will not affect the child's relationship with this hospital. Parent information and consent forms have been drafted and are attached to this application. The serology performed on those who agree to the test will be informed of their anti-pertussis antibody titre and what that means to their immunity against pertussis. This would be of benefit in terms of preventing spread of pertussis within the family/household by immunisation. Non-immune individuals will be advised to be immunised. Additionally, participants are free to contact Michelle Cagney or Dr Raina MacIntyre if they have any concerns. NCS Australasia are experienced in health surveys and may also be available to help with distressed parents during the interviews.

Review of progress

Weekly survey updates will be supplied by NCS Australasia for preliminary analysis and approach of parents re the serologic survey. It is not envisioned that there will be any need to prematurely terminate the study.

Management of adverse events

Concerned parents are encouraged to call NCIRS if they think that their child has been adversely affected by participation in this study. If the child becomes ill or is injured as a result of participation, then reasonable costs of medical treatment will be paid by the Children's Hospital at Westmead

Winding up procedures

This study does not involve any long-term, on-going care of participants. Feedback from this study to participating families will be in terms of their child's antibody levels against pertussis. The serology performed on those who agree to the test will be informed of their anti-pertussis antibody titre and what that means to their immunity against pertussis. This would be of benefit in terms of preventing spread of pertussis within the family/household by immunisation. Non-immune individuals will be advised to be immunised.

Access to data

Data will be kept on password protected computer files for the duration of the research. Hard copies of the questionnaire will be kept in a locked filing cabinet. Only the study investigators will have access to the computer and paper files. The computer files will be kept long term in a password protected database. All identifying data will be coded and de-identified for participant's privacy.

Will data be collected from a government agency?

No data will be obtained from any government agency for use in this study.

Storage or disposal of data

Data will be kept on password protected computer files for the duration of the research. The computer files will be kept long term in a password protected database. Hard copies of the questionnaire will be kept in a locked filing cabinet. The paper files will be retained for five years and will be disposed of using a document shredder.

DECLARATION

We undertake to carry out the research project (Survey of cough and pertussis immunisation status in children) as described in this application and to comply with the general and specific conditions laid down by the Ethics Committee.

We do not have a commercial interest in the outcome of this study

We also undertake to notify the Ethics Committee should any changes to the protocol be necessary, should any unexpected complications or adverse events take place, or should the study be abandoned for any reason.

The results of the study will be reported to the Ethics Committee annually during the course of the study and at its conclusion. A copy of any abstracts or publications resulting from the project will be submitted to the Research and Development Office.

Signatures:

Dr Raina MacIntyre _____   Date _____

Dr Peter McIntyre _____   Date _____

Ms Michelle Cagney _____   Date _____

Ms Siranda Torvaldsen _____   Date _____

NSW Cough Survey Questionnaire

"Hello, my name is _____. I am calling about an important study on chest problems and immunisation in children aged 5–14 years in Western Sydney, on behalf of the New Children's Hospital at Westmead. We would like to interview the person most involved with the children in the household. We don't need to know any names or personal details. Could you spare a little time to answer some quick questions?

1 Agreed → go to question CIN1

2 Refused → EXIT

3 Business → EXIT

4 Institution → EXIT

5 Fax machine → EXIT BUT COME BACK FOR ONE CALL BACK

6 Answering machine → EXIT BUT COME BACK FOR ONE CALL BACK

7 No answer → EXIT

8 Not a resident of WSAHS → EXIT

9 Hang up – thinks we want money →CALL BACK

10 No children aged 5–14 years → EXIT

CIN1 Thank you very much. The study will help us in understanding some common chest problems in children. Just to let you know, your phone number has been randomly selected from the phone numbers in your area.

CIN2: Do you have any children aged 5 to 14 years that usually live in this household? ("live in this household" means all 5 days of the school week)

Yes   1   → go to CIN3

No   2   → thank you but this study is only about children aged 5–14, goodbye

Refused   3 → Encourage to participate

CIN3 How many children live in the household?

a. Fixed number _____

b. Variable number → go to CIN4

CIN4 If the number of children living in the household varies, could you tell me why?

CIN5 We would appreciate your involvement in this study, is now a convenient time?

Yes → go to CIN6

No, now is not a good time → make an appointment

Refusal → encourage to participate

CIN6

IF ONE ELIGIBLE CHILD: Automatic selection of that child

IF MORE THAN ONE ELIGIBLE CHILD: We are collecting information about one child from each selected household and now we would like to select that child.

Select child whose birthday is next.

We would like to interview the parent/carer of the child X. Could I have that child's first name? _____ (you can use a pretend name for the interview)

CIN7 Because this survey is about child health we need to speak to the parent or carer who knows most about the child's health. Is that you?

(If necessary prompt: "knows most" is the one who took to child to get immunised or to the doctor when the child was sick)

 1 Yes: I know most about the child's health

 3 No: I'll get them

 4 No: not at home at present → make an appointment

 5 Refusal: ENCOURAGE TO PARTICIPATE → ask for reason

   why_____ → thank you and goodbye→ exit

 6 Unavailable for duration of survey → exit

 7 Main carer doesn't speak English → Which language? _____→thank you

   and goodbye→ exit

CIN8 What is your relationship to the child?

Mother

Father

Stepmother

Stepfather

Grandmother

Grandfather

Sibling

Legal guardian

Other _____

Don't know

Refused

Section 1:Questions about cough

COU1 Has your child been diagnosed with having any of the following illnesses by a doctor or at a hospital?

a. Pneumonia ever

Yes   1   (go to pn1)

No   2   ⎤
             ⎬ go to COU 1b
Unsure   3   ⎦

pn1: how many times has your child been diagnosed with pneumonia?

Once   1

More than once   2

Answer the below questions for the most recent episode.

pn2: What year was this (or how old was your child)   _____

pn3: Was your child admitted to hospital for pneumonia?

Yes   1

No   2   ⎤
             ⎬ go to COU 1a pn5
Unsure   3   ⎦

pn4: Length of stay:

Overnight

More than one night

pn5: Where was pneumonia diagnosed:

Doctor's surgery

Hospital: ward

Hospital: emergency department

Other (including self) _____

pn6: Was your child given antibiotics?   Yes   1   No   2   Unsure   3

pn7: Was a chest x-ray done?   Yes   1   No   2   Unsure   3

b. Bronchitis in the last year?

Yes   1

No   2   ⎤
            go to COU 1c
Unsure   3 ⎦

Was hospital admission required   Yes   1   No   2   Unsure   3

c. Whooping cough ever?

Yes   1

No   2   ⎤
            go to COU 1d
Unsure   3 ⎦

wc1: How many times was your child diagnosed with whooping cough? Answer the below questions for all episodes

wc2: What year was this (or how old was your child)?   _____

wc3: In what month was whooping cough diagnosed? _____

wc 4: Was hospital admission required   Yes   1   No   2   Unsure   3

wc5: What, if any, were done for whooping cough (one or more)?

     Blood test

     Nose swab

     Yes, but unsure of the test

     Other

     No tests were done

     Unsure

wc6: Which, if any, of the tests show whooping cough (one or more)?

     Blood test

     Nose swab

     Yes, but unsure of the test

     Other

     No tests showed whooping cough

     Unsure

d. Croup in the last year?

Yes   1

No   2   go to COU 1e

Unsure   3

Was hospital admission required   Yes 1   No 2   Unsure 3

e. Asthma ever?

Yes   1

No   2   go to COU 1f

Unsure   3

as1 Age at diagnosis   _____ years

as2 Was this in the last year   Yes 1   No 2   Unsure 3

as3 Was hospital ever required   Yes 1   No 2   Unsure 3

as4 Has your child needed to take any asthma medication or "puffer" (such as ventolin, flixotide or atrovent) in the last year?

Yes 1   No 2   Unsure 3

as5 How many episodes of wheezing has your child had in the last year? _____

f. Has your child ever been diagnosed with any other lung problem ?

If yes → Please specify: Diagnosis

                Cystic fibrosis

                Pleurisy

                Pneumothorax

                Pleural effusion

                Bronchiestasis

                Tuberculosis

                Bronchiolitis

                Allergic bronchopulmonary aspergillosis

                Lung transplant

                Bronhopulmonary dysplasia (Hyaline membrane

                disease/chronic lung disease of infancy)

                Post-cancer or post-cancer therapy lung disease

                Foreign body

                Pneumocystis carinii Pneumonia

                Immotile ciliary syndrome

                Other, please specify _____

No   2   ⌉ go to COU 1g

Unsure   3   ⌋

g. Does your child have any other long-term health problem(s) which he/she has to visit a doctor or hospital regularly for?

Yes   1

No   2→ go to COU2

Unsure   3→ go to COU2

If yes → Please specify: Diagnosis _____

COU2 Has your child had a continuous cough that lasted for 2 weeks or more in the last year?

Yes   1

No   2→ go to section 2

Unsure   3→ go to section 2

COU3   On how many occasions did your child have a cough of 2 weeks or more followed by at least 1 week without coughing?

a. Once   1

b. More than once   2

COU4

a. How many weeks was the longest coughing illness your child had in the last year? _____ weeks

b. Do you remember what month of the year in which the cough started? _____

COU5   During this or these coughing illness(s) in the last year, did your child experience any of the following?

a. Wheeze   Yes   1 → go to COUa1

                            No   2→ go to COU5 b

                            Unsure   3→ go to COU5 b

a 1: If yes, did your child's wheezing frequency change during the coughing illness?

Yes   1

No   2

Unsure   3

b. A visit to the doctor about the cough   Yes   1

No   2

Unsure   3

c. Pains in the muscles and joints   Yes   1   No   2   Unsure   3

d. Bursts of coughing for minutes at a time   Yes   1   No   2   Unsure   3

e. Rash   Yes   1   No   2   Unsure   3

f. Nasal congestion   Yes   1   No   2   Unsure   3

g. Coughing so hard that he/she had to draw breath suddenly (a whoop)

Yes   1   No   2   Unsure   3

h. Fever   Yes   1   No   2   Unsure   3

i. Sore throat   Yes   1   No   2   Unsure   3

j. Sore ribs/chest/back due to coughing?   Yes   1   No   2   Unsure   3

k. Shortness of breath   Yes   1   No   2   Unsure   3

l. Coughing followed by vomiting   Yes   1   No   2   Unsure   3

m. Fever	Yes	1	No	2	Unsure 3
n. Headache	Yes	1	No	2	Unsure 3
o. Sinus	Yes	1	No	2	Unsure 3
p. Night cough	Yes	1	No	2	Unsure 3
q. Fatigue	Yes	1	No	2	Unsure 3
r. Flushed face	Yes	1	No	2	Unsure 3
s. Did the coughing bring anything up?	Yes	1	No	2	Unsure 3
t. Hoarseness or loss of voice	Yes	1	No	2	Unsure 3

u. Stopped breathing for a short time following coughing

<div style="text-align:right;">Yes 1   No 2   Unsure 3</div>

v. Going blue about the mouth following coughing

<div style="text-align:right;">Yes 1   No 2   Unsure 3</div>

COU6   This question only for those who answered "yes" to question COU 5b: What was the coughing illness diagnosed as?

       Asthma (do logic check)

       Pneumonia (do logic check)

       Viral illness (do logic check)

       Bronchitis (do logic check)

       Sinusitis (do logic check)

       Whooping cough (do logic check)

       Laryngitis (do logic check)

       Upper respiratory tract infection (do logic check)

       Other _____

COU7 In the month before your child started coughing, had he/she been around
anyone else who had:

a. a troublesome cough   Yes   1 → COU8

                                          No   2 ⎫
                                                   ⎬ go to COU 7b
                                          Unsure   3 ⎭

b. been recently diagnosed with whooping cough?

                          Yes   1 → COU 9

                          No   2 ⎫
                                    ⎬ go to COU 10
                          Unsure   3 ⎭

COU8 What is the relation of that person to your child?

Mother/stepmother

Father/stepfather

Legal guardian

Sibling

Grandparent

School mate

Teacher

Other _____

COU9 What is the relation of that person to your child?

Mother/stepmother

Father/stepfather

Legal guardian

Sibling

Grandparent

School mate

Teacher

Other _____

COU10 After your child started coughing, did anyone else:

a. develop a troublesome cough   Yes   1 → COU13

                            No   2   go to COU10b

                            Unsure   3

b. have a diagnosis of whooping cough?

                            Yes   1 → COU14

                            No   2   go to section 2

                            Unsure   3

COU13 What is the relation of that person to your child?

Mother/stepmother

Father/stepfather

Legal guardian

Sibling

Grandparent

School mate

Teacher

Other _____

COU14 What is the relation of that person to your child?

   Mother/stepmother

   Father/stepfather

   Legal guardian

   Sibling

   Grandparent

   School mate

   Teacher

   Other _____

Section 2: Demographic questions: children 5–14 years

DEM1 What is your child's date of birth? _ _ /_ _ /19 _ _

If respondent does not wish to give DOB, ask:

What was your child's age at his/her last birthday? _____ years

DEM2 Is your child male or female?

   Female   1

   Male   2

DEM3 Residence:

a. What is the postcode of your usual address?   _____

  (Normally means in the preceding school year)

b. What suburb do you usually live in? _____

DEM4 In which country was your child born?

Australia → go to DEM5

New Zealand

Pacific Islands   go to DEM 6

Asia

Europe

Africa

North America

South America

Other _____

DEM5 Is your child of Aboriginal or Torres Strait Islander origin?

Yes   1

No   2

Unsure   3

DEM6 Does your child speak a language other than English? (use full list of languages)

        Arabic

        Chinese

        Italian

        Greek

        Spanish

        Filipino

        Other _____

DEM7 What type of educational institution (if any) does your child attend?

        Preparatory school

        Kindergarten

        Primary school

        Secondary school

        None

        Refused

DEM8 How many other people live in your household other than (name of surveyed child)? _____

Number of children younger than _____ (name of surveyed child)

Number of children older than _____ (name of surveyed child)

Number of parents _____

Number of other adults _____

SECTION 3: Social context and Smoke exposure

SE1 Does anyone in the household have a Health Care Card?

Yes	1
No	2
Unsure	3
Refused	4

SE2 Does anyone in the household smoke?

Yes	1
No	2
Unsure	3
Refused	4

Section 4:Questions about immunisation

VAC1: We will ask you to refer to your child's immunisation records (such as the "blue book") later in the questionnaire, are you able to get these?

Yes, I can get it now → go to VAC 2

1

Yes, but it will take some time → Get a time to call them back

2

No → Let them know that it is not essential and encourage to continue

3

Refused

4

The next few questions are about your child's immunisation. The whooping cough immunisation is usually given to babies and preschool children in the same needle as diphtheria and tetanus and is called the "DTP" or "Triple antigen" vaccine. It is possible some children were not immunised against whooping cough and were only given a vaccine for diphtheria and tetanus known as the "CDT" vaccine.

VAC2 Did your child ever receive any vaccinations against whooping cough?

Yes	1 → go to VAC 4
No	2 → go to VAC 3
Unsure	3 → go to VAC 4

VAC3 What were your reasons for not vaccinating your child against whooping cough?

I don't believe in immunisation/ disagree with immunisation

Medical reasons

Religious reasons

Out of country

Doctor didn't offer the immunisation

Forgot

Other _____

Refused

 Now go to VAC8

VAC4 Do you have your child's immunisation records in front of you?

Yes   1

No   2 → Encourage them to continue on, trying to recall the dates of immunisation

VAC5 Has your child received:

   The first dose due at approximately 2 months of age:

        Yes   1

Date of first dose and type from record   _ _/_ _/19 _ _ CDT

DTP

Recalled date and type of vaccine   _ _/_ _/19 _ _ CDT

Or age__   DTP

No   2

Unsure   3

Refused   4

The second dose due at approximately 4 months of age:

Yes   1

Date and type of second dose from record   _ _/_ _/19 _ _ CDT
DTP

Recalled date and type of vaccine   _ _/_ _/19 _ _ CDT

Or age__   DTP

No   2

Unsure   3

Refused   4

The third dose due at approximately 6 months of age:

Yes   1

Date and type of third dose from record   _ _/_ _/19 _ _ CDT
DTP

Recalled date and type of vaccine   _ _/_ _/19 _ _ CDT

Or age__   DTP

No   2

Unsure   3

Refused   4

The fourth dose due at approximately 18 months of age:

Yes   1

Date and type of fourth dose from record   _ _/_ _/19 _ _ CDT
DTP

Recalled date and type of vaccine   _ _/_ _/19 _ _ CDT

Or age__   DTP

No   2

Unsure   3

Refused   4

For children who turned 6 years in 1995 or later:

Did your child receive the fifth dose vaccine due at approximately 4 years of age or just before school entry:

Yes   1

Date of fifth dose from record   _ _/_ _/19 _ _

Recalled date   _ _/_ _/19 _ _ or age

No   2

Unsure   3

Refused   4

For children who turned 4 years old in 1997 or later:

The new "acellular" whooping cough vaccine became available in the middle of 1997. Until the beginning of 1998 having your child immunised with the acellular vaccine would have incurred an extra cost. Do you know the name of the vaccination your child received as the fifth dose?

(PROMPT: did you pay for the 5th dose?)

What type of vaccination did your child receive as the 5th dose?

Whole cell DTP/'Triple antigen'   1

CDT   2

Tripacel (or acellular DTP)   3

Infanrix (or acellular DTP)   4

Unsure   5

Other   6

The following two questions concern possible side effects following the whooping cough vaccine:

VAC6 Did your child experience any side effects or reactions following the whooping cough vaccination, including redness and swelling about injection site, pain in arm where they had the needle, fever, irritability, inconsolable crying, loss of appetite?

Yes	1 → go toVAC7
No	2→ go toVAC8
Unsure	3 → go toVAC8

VAC7

Which of these reaction(s) did your child have in the day or two following the whooping cough immunisation? (One or more answers):

> Redness about injection site
>
> Swelling about injection site
>
> Pain in arm where they had the needle
>
> Fever
>
> Irritability
>
> Inconsolable crying
>
> Loss of appetite
>
> Other, please specify _____

Did you seek medical attention for the reaction?

Yes	1
No	2
Unsure	3

With what dose did your child have a reaction?

Dose 1	1
Dose 2	2
Dose 3	3
Dose 4	4
Dose 5	5
All doses	6
More than one dose	7
Unsure	8

ASK ALL:

VAC8 I would like to thank you for your time and co-operation with this survey. Would you mind to having one of the members from the Children's research team contact you in the next couple of months? This will be about participation in further research on childhood coughs. They will explain more when they get in touch.

Yes:

Name of person to contact _____

Phone number _____

Preferred time to call: Day/Evening

Child's name _____

No   2

END OF QUESTIONNAIRE

Appendix 2

Effectiveness of pertussis vaccination in New South Wales, 1996 to 1998

Effectiveness of pertussis vaccination in New South Wales, Australia, 1996 to 1998

Siranda Torvaldsen[1]

Judy M Simpson[2]

Peter B McIntyre[1]

[1] National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases

[2] Department of Public Health and Community Medicine, University of Sydney

Corresponding author:

Siranda Torvaldsen

National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases

The Children's Hospital at Westmead

Locked Bag 4001

Westmead   NSW   2145

Tel: +61 2 9845 3062

Fax: +61 2 9845 3082

Email: SirandaT@chw.edu.au

Summary

Background: Notifications of pertussis have increased recently in Australia and other industrialised countries. This study estimates the effectiveness of pertussis vaccination in New South Wales children aged less than 14 years, during a period when an Australian whole-cell pertussis vaccine was in routine use.

Methods: Cases notified with pertussis between 1996 and 1998 and pertussis vaccine coverage estimates from the Australian Childhood Immunisation Register were used. Vaccine effectiveness (VE) was calculated using the screening method in a logistic regression model which included age group, year of disease onset and area of residence.

Results: VE was highest (91%) in the youngest age group (8-23 months) and lowest (78%) in the oldest age group (9-13 years). VE estimates were lower in 1998 than in the previous two years, particularly in one area.

Conclusions: Pertussis vaccination, primarily with the Australian whole-cell pertussis vaccine, is highly effective at preventing pertussis in New South Wales children, as measured by notified cases. Although the screening method has many potential biases, trends in VE may still be monitored over time assuming these biases remains constant. Such ongoing monitoring will be important to evaluate VE following Australia's change to an acellular vaccine based program. The approach described here enables this to be incorporated into routine surveillance.

Keywords: vaccine effectiveness, pertussis, screening method

Introduction

Pertussis (whooping cough) is the most important vaccine preventable disease, in terms of morbidity and mortality, in Australia[1] and many other industrialised countries. In addition to the analysis and interpretation of disease surveillance and vaccination coverage data, there is a need for a monitoring system capable of detecting major shifts in the effectiveness of the pertussis vaccination program. Further indications for monitoring pertussis vaccine effectiveness (VE) include evidence of a major change in VE elsewhere,[2] a lack of effectiveness data for the whole-cell vaccine previously used in Australia and the recent introduction of acellular vaccines. In Australia, pertussis vaccines are given with diphtheria and tetanus (DTP) at two, four and six months of age with a booster at 18 months of age. In 1994, a fifth dose of DTP was introduced, initially at 4-5 years and subsequently at 4 years of age. A whole-cell vaccine, produced in Australia, was used exclusively until 1997, when acellular pertussis vaccines became available. In 1998, acellular vaccines replaced the whole-cell vaccine for the fourth and fifth dose and in 1999 for all doses.

This study aims to estimate the effectiveness of the primary course (doses 1-3 due at 2, 4 & 6 months of age) of the pertussis vaccination program in New South Wales (NSW) children between 1996 and 1998, using the screening method. During this time period the whole-cell vaccine accounted for the great majority of pertussis vaccines used. The screening method compares the proportion of cases who are vaccinated (PCV) with the proportion of a comparable group in the population who are vaccinated (PPV). It is a simple and rapid method which has been used to estimate pertussis VE in Nova Scotia,[3] the United Kingdom,[4] the United States,[5] New Zealand[6] and the Netherlands.[2] In Australia it has been used to estimate the effectiveness of *Haemophilus influenzae* type b vaccination[7] but not pertussis vaccination.

Methods

Study Subjects

All cases of pertussis notified to NSW Health from January 1, 1996 to December 31, 1998 aged less than 14 years at the date of disease onset were selected from the

Notifiable Diseases Database (NDD) of the NSW Department of Health. Cases aged less than eight months were excluded to allow time for infants to complete the primary vaccination schedule for pertussis.

The NDD includes information on the method of pertussis diagnosis and the number of doses of vaccine received, but not date of vaccination or type of vaccine administered (whole-cell or acellular). In this study, fully vaccinated cases are defined as in receipt of at least three doses of a pertussis-containing vaccine. Incompletely vaccinated children were excluded from VE analyses which were comparisons of fully vaccinated with unvaccinated groups, as described by Orenstein.[8]

NSW is divided into eight rural and nine metropolitan health areas. Health areas in which vaccination status was not recorded for more than 25% of notified cases were excluded. Some geographically adjacent areas were combined. The areas studied include three metropolitan (Central & South Eastern Sydney, Western Sydney, and Wentworth) and two rural areas (Southern & Greater Murray, and Northern Rivers), which together comprise 46% of the NSW population.

Population estimates

Population coverage estimates were taken from the Australian Childhood Immunisation Register (ACIR). The ACIR contains information on the vaccination status of children born since January 1, 1996 (when the register commenced), who are either registered with the universal health insurer in Australia (Medicare) or have had a vaccination encounter reported by a vaccine provider to the ACIR.[9] A 12-month cohort of 87 564 children born between 01/04/97 and 31/03/98 was selected from the ACIR and vaccination status at 12 months of age assessed as of 31/03/99. This time period was chosen to allow sufficient time since the ACIR commenced for accurate population estimates of immunisation coverage. Health area was determined by postcode of residence. PPV for each area was calculated by dividing the number of children fully vaccinated by the sum of the number of children fully vaccinated and unvaccinated (that is, incompletely vaccinated children were excluded). It was assumed that PPV did not change over the study time period.

VE estimation

VE was estimated by fitting a logistic regression model using the method described by Farrington, whereby the number of vaccinated cases is treated as derived from a binomial distribution, with PCV as the parameter and number of cases (N) as the index.[10] *Proc Genmod* in the software package SAS[11] was used for modelling. Logit PPV was specified as an offset in the model, and the variables age group, health area of residence and year of disease onset were included as potential confounders. The base model containing the three potentially confounding variables was fitted and the significance of each one tested (using the type3 option in SAS). The effects of all 2-way interactions were tested for statistical significance ($p < 0.05$) by adding them in turn to the base model. VE was calculated for each combination of age group, area and year by subtracting the exponentiation of the estimated linear predictor (XBETA in SAS) from one. Confidence intervals were calculated in a similar way using the standard error of the linear predictor (STD in SAS).

In order to obtain overall estimates by area and age group, the average of the relevant parameter estimates for year, including the interaction terms, was calculated. To obtain overall estimates by year and age group, the parameter estimates for area, including the interaction terms, were weighted by population. The adjusted estimates of year and area were used to calculate VE for each age group, adjusted for year and area. The variances of these adjusted parameter estimates were calculated from the covariance matrix using Excel.[12] Confidence intervals were calculated using these variances.

Results

Pertussis notifications

In NSW from 1996 to 1998, 3371 cases of pertussis in children aged 8 months to 13 years from a known health area were notified. Of the 3371 cases, 1609 cases (48%) were resident in areas which were included in VE analyses. There was considerable variation among health areas in both notification rate and vaccination status of cases (Figure 1). After excluding the 256 cases whose vaccination status was unknown and the 75 cases who had received only one or two doses of the vaccine, there were 1278 notified cases eligible for the VE analyses. 1997 was an epidemic year for pertussis in

NSW, with most areas experiencing an epidemic that year. Of the 1278 eligible cases, 810 (63%) had a date of onset in 1997.

Of the 1278 cases eligible for inclusion in the study, 6% were diagnosed based on a positive culture result, 70% on serology, 23% clinically and in 1% of cases the method of diagnosis was unknown. The proportions diagnosed by culture decreased with increasing age, from 30% in children aged less than two years to 4% in children aged 9-13 years, whilst the proportions diagnosed by serology increased with increasing age.

Vaccination status of notified cases

Of the 1278 cases eligible for inclusion in the study, 762 (60%) had received at least three doses of a pertussis-containing vaccine. Most (92%) of the vaccinated cases aged two years or older had received a fourth dose, while 51% of vaccinated 5-8 year olds and 21% of vaccinated 9-13 year olds had a fifth dose of vaccine recorded.

Population estimates

Vaccination coverage varied by area, with Southern and Greater Murray health areas having the highest coverage and Northern Rivers having the lowest (Table 1).

The model

The final model included age group, year of onset and health area, plus the interaction between health area and year. This model had a deviance of 46 with 42 degrees of freedom, suggesting that the model is an adequate fit of the data (p=0.3). In this model all variables were significant (p<0.001).

Age group

Age group was highly significant in the base model (χ_3^2=20, p<0.0001). The VE estimate, after adjustment for area and year, was highest in the 8 to 23 month age group and lowest in the 9 to 13 year group (Table 2).

Health area and year of onset

Health area was the most significant term in the base model (χ_4^2=91, p<0.0001) followed by year of onset (χ_2^2=41, p<0.0001). The interaction between year and area

was also highly significant (χ^2_8 =28, p=0.0004). Estimates by area, adjusted for year (Table 3) and by year, adjusted for area (Table 4), were calculated.

The 1998 VE estimates were considerably lower than the 1996 and 1997 estimates (Table 4). This effect was most marked in the Greater Murray/Southern area. When the model was run with the Greater Murray/Southern area excluded, the interaction term was no longer significant (p=0.6). Following removal of the interaction term, year accounted for less of the variability but was still significant (χ^2_2 =6.3, p=0.04), and the 1998 VE estimates remained the lowest.

Discussion

This study shows that pertussis vaccination is highly effective at preventing pertussis in NSW children as it is measured by notified cases. The estimates in this study are not vaccine-specific but largely represent whole cell vaccines, as acellular pertussis vaccines have only been available free of charge for use in the primary course since February 1999.[1] The 1996 and 1997 VE estimates calculated in this study are similar to those reported in a New Zealand study which applied the screening method to notification data from the 1996 pertussis epidemic.[6]

The degree to which notified cases represent all pertussis cases was not evaluated, but notified cases are clearly not a random sample and are likely to represent the more severe end of the disease spectrum. Over three-quarters of the notifications were laboratory confirmed, mostly by serology. Although not undertaken on these data, the effect of including only laboratory confirmed cases on VE estimates using pertussis notifications from 1993 to 1998 was examined.[13] Including only laboratory confirmed cases slightly increased the VE estimates. The greatest increase was in the youngest age group who also had the greatest proportion of culture confirmed cases. Previous studies have found that increasing the specificity by including only clinically severe or culture positive has increased the VE estimates.[8,14]

Since the early 1990s, a commercially available enzyme-linked immunosorbent assay (ELISA) for IgA against whole-cell *B. pertussis* has been widely used in diagnostic laboratories throughout Australia. Although the validity of these tests are difficult to

evaluate without a diagnostic reference standard, a study undertaken in western Sydney found that cases notified on the basis of positive whole-cell serology had symptoms clinically consistent with pertussis almost uniformly, suggesting that notifications based on positive serology under-estimate, rather than over-estimate, the true incidence of pertussis.[15]

Although this study aimed to measure the effectiveness of three doses of a pertussis-containing vaccine, most cases who had received three doses and were eligible for a fourth dose had received it. Assuming that four doses of the vaccine is more effective than three doses, the effectiveness of three doses may have been over-estimated. Half of the cases in the 5 to 8 year old age group had received fifth dose. In the future we would expect this proportion to rise with a corresponding increase in the VE estimate, both overall and relative to the 9 to 13 year olds.

Possible sources of bias

Cases

Cases with unknown vaccination status give rise to a potential selection bias. It is possible that cases who were not as readily followed up to check their vaccination status were less likely to be fully vaccinated than cases who were able to be followed up. However, excluding health areas where the vaccination status of a large proportion of cases was unknown minimises this bias. As parental recall generally over-estimates vaccination coverage, vaccination status of cases is more likely to be misclassified as vaccinated.[16] This would lead to an under-estimate of VE.

Where VE estimates are derived from notifications, detection bias (ie the tendency to suspect pertussis less in persons known to be fully vaccinated) is an important potential problem leading to falsely high VE estimates.[4] Although we are unable to determine the importance of this bias in NSW notifications, with the exception of possible increased reporting during epidemics, we would expect its effect to be reasonably constant over time.

Coverage estimates

The ACIR did not commence operation until January 1996 so estimates of coverage are not available for all years in the study period. The cohort used for estimation of PPV was chosen in preference to earlier cohorts to allow time for improvement in reporting of vaccinations to the ACIR. Although estimates from the ACIR show that overall coverage with 3 doses of DTP in NSW increased from 75% in March 1997 (the first cohort) to 84% in December 1998, most of this increase is believed to be due to increased reporting. It should be noted that the PPV values were incorporated into the model as fixed values, therefore the confidence intervals only relate to the error of the linear predictor and do not incorporate any error around the PPV values.

Underestimation of vaccination coverage will tend to reduce VE estimates.[5] The ACIR data most likely under-estimate current coverage due to incomplete reporting of vaccination status.[9] However, if coverage has improved over the study period then the ACIR estimates used are most likely to have over-estimated coverage in the earlier part of the study period and in the older age groups. If coverage has increased, possibly due to a number of incentive schemes introduced by the Commonwealth Government since 1997,[17] then this may be at least partly responsible for the apparently lower VE in 1998. Reporting to the ACIR may vary between health areas and could account for some of the regional differences in VE estimates. Coverage may have improved over the study period differentially between areas, which could explain the significance of the interaction between health area and year. From the results it seems likely that coverage increased more in the Greater Murray/Southern area than in other areas, if coverage increased at all in other areas.

Age

VE estimates were consistently highest in the youngest age group and lowest in the oldest age group. If true vaccine coverage was lower in the oldest age group then the VE estimates would be reduced even further in this group. Age is a proxy measure for time since vaccination. Vaccine-acquired immunity wanes with time[18,19] so it is not surprising that VE is lowest in the older children. These results, together with the increasing median age of notified cases in Australia,[1] suggest that childhood vaccination against pertussis is less effective against disease in adolescence.

Area

Much of the variation in VE between areas could be due to inaccuracies in coverage estimates for some or all of the study period. However, differences in notification practices, handling and storage of vaccines and levels of exposure to pertussis may also account for some of the differences in VE. A comparison of NSW infant pertussis hospitalisation and notification data by health area suggests that some of the differences in notification rates between areas reflect differences in notification practices, as opposed to differences in pertussis incidence.[13]

Year

The VE estimates, adjusted for area, in 1998 were generally lower than in the previous two years, particularly in the Greater Murray/Southern area. The population coverage figures used in the model may be a more accurate reflection of true coverage in 1998 than in previous years. If this is the case, then the 1998 VE estimates are more realistic than those for 1996 and 1997. A study using similar methodology in the United States estimated pertussis VE between 1994 and 1996 in 7-18 month old children to be 82%,[5] the same as our 1998 estimate in the youngest age group. Alternatively, coverage may have improved over the three year period with coverage being under-estimated for 1998, thus resulting in an under-estimate of VE in 1998. The most likely scenario lies somewhere in between these two alternative explanations, that is coverage has improved and was over-estimated for the years 1996 and 1997 and under-estimated for 1998. It is also possible that differences in VE over the time period are due to differences in notification practices, although we have no evidence of changes to the notification system.

The possibility that VE did actually decrease in 1998 should not be completely dismissed. A recent paper from the Netherlands reported a downward trend in VE and in 1997, the final year in which VE was analysed, the PCV exceeded the PPV.[2] Although there is no evidence of a mismatch of the vaccine strain and the circulating *Bordetella pertussis* strains in Australia, the ongoing surveillance of pertussis, including VE, is of paramount importance.

Conclusion

Although the extent to which notified childhood cases of pertussis represent all childhood cases of pertussis is not known, the results of this study suggests that the pertussis vaccination program is highly effective, especially in younger children. Whilst the potential for biases inherent in the screening method is substantial, this approach has been used extensively elsewhere and is particularly useful for monitoring trends in VE, provided any bias remains constant over time. The strength of this methodology lies in its ease of application and the fact that it could be incorporated into routine surveillance of vaccine preventable diseases.

As the ACIR matures, checking the immunisation status of cases in Australia will be easier and the population estimates more accurate. In addition, it will be possible to use the population coverage data of the cohort of children from which the cases arose, which will improve the precision of the VE estimates. In contrast to the previous studies which have used the screening method to estimate pertussis VE,[2-6] we have been able to use regional coverage data. Although logistic regression has been used in one previous screening method study which included year and age as potential confounders, it did not include area or use area-specific population coverage values.[4] In the United Kingdom it was felt that the use of national coverage data may have produced artificially high VE estimates[4] and Farrington illustrates the confounding effect of pooling population coverage data.[10] In Australia, the regional coverage data available from the ACIR should be incorporated in all future pertussis VE studies which use the screening method. This will be particularly important in monitoring the impact of the change to acellular pertussis vaccines as well as shifts in vaccine effectiveness possibly attributable to other factors such as population shifts in prevalent strains of *Bordetella pertussis*.

Acknowledgements

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Figure 1. Pertussis notifications by health area and vaccination status in NSW children aged 8 months to 13 years, 1996-1998
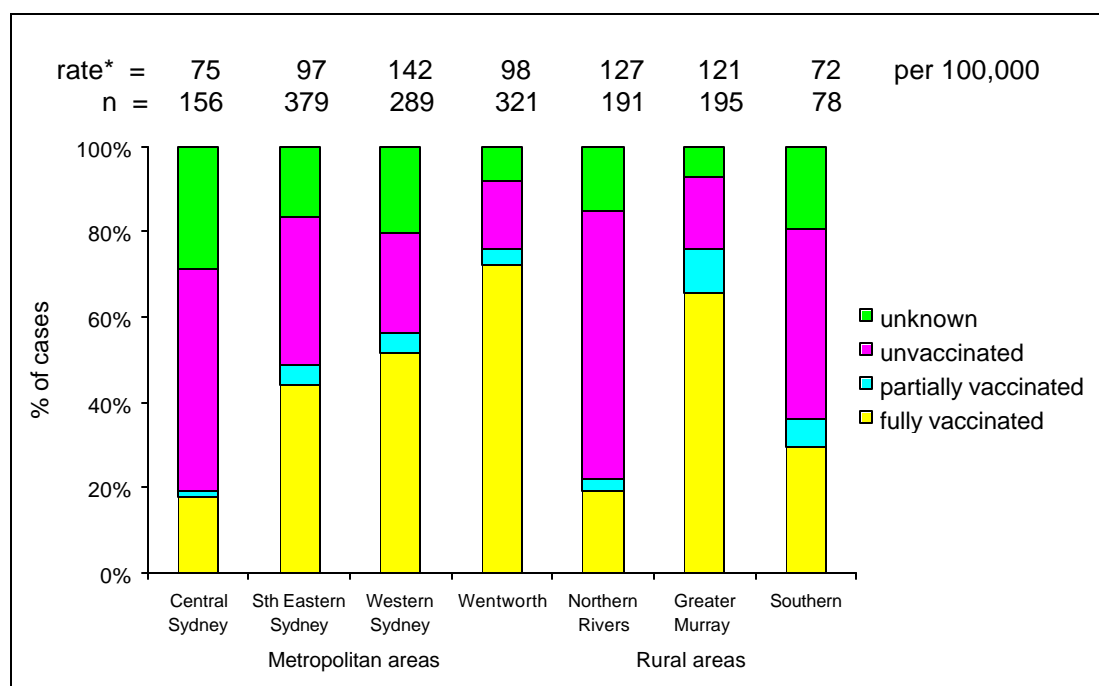
*Average annual notification rate per 100,000 population aged 8 months to 13 years

Table 1. Pertussis vaccination coverage by NSW health area(s) for children aged 12 months of age, 1996-1998

Health area(s)	% fully vaccinated*	% partially vaccinated[†]	% unvaccinated[‡]	PPV (full/(full+none))
Central & SE Sydney	82	8	10	0.893
Western Sydney	83	9	7	0.920
Wentworth	87	7	6	0.939
Northern Rivers	81	10	10	0.893
Greater Murray & Southern	88	8	4	0.957
Total	85	8	6	0.930

*3 doses, [†]1-2 doses, [‡]0 doses

Table 2. VE estimates by age group, adjusted for year and NSW health area, 1996-1998

	Vaccinated cases (PCV %)	Total cases	VE (%)	95% CI (%)
8 to 23 month olds	39 (49)	80	91.0	85.5 to 94.4
2 to 4 year olds	106 (55)	192	84.5	78.3 to 88.9
5 to 8 year olds	223 (53)	421	86.5	82.7 to 89.5
9 to 13 year olds	394 (68)	577	77.6	71.7 to 82.3

Table 3. VE estimates by NSW health area(s) and age, adjusted for year, 1996-1998

	Vaccinated cases	Total cases	VE (%)	95% CI (%)
8 to 23 month olds				
Central & SE Sydney	5	20	93.9	89.5 to 96.5
Northern Rivers	6	15	96.8	93.7 to 98.3
Western Sydney	13	16	88.9	81.1 to 93.5
Wentworth	9	15	83.0	68.8 to 90.7
Southern & Greater Murray	6	14	96.0	94.5 to 97.1
2 to 4 year olds				
Central & SE Sydney	24	53	89.6	83.8 to 93.3
Northern Rivers	10	32	94.4	90.2 to 96.8
Western Sydney	33	52	80.9	70.7 to 87.6
Wentworth	23	30	70.7	50.7 to 82.6
Southern & Greater Murray	16	25	93.1	89.1 to 95.7
5 to 8 year olds				
Central & SE Sydney	51	114	90.9	87.0 to 93.7
Northern Rivers	10	69	95.1	91.7 to 97.2
Western Sydney	65	94	83.4	76.0 to 88.5
Wentworth	51	68	74.5	59.5 to 84.0
Southern & Greater Murray	46	76	94.0	91.2 to 95.9
9 to 13 year olds				
Central & SE Sydney	89	175	84.9	78.7 to 89.3
Northern Rivers	11	41	91.9	86.2 to 95.3
Western Sydney	85	116	72.4	60.1 to 80.9
Wentworth	126	141	57.7	33.9 to 72.9
Southern & Greater Murray	83	104	90.1	85.5 to 93.2

Table 4. VE estimates by year and age, adjusted for health area

	Vaccinated cases	Total cases	VE (%)	95% CI (%)
8 to 23 month olds				
1996	5	19	94.2	89.9 to 96.6
1997	26	54	93.0	88.7 to 95.7
1998	8	15	82.0	68.5 to 89.7
2 to 4 year olds				
1996	14	32	90.0	84.3 to 93.6
1997	63	124	88.0	83.1 to 91.4
1998	29	36	69.2	51.4 to 80.4
5 to 8 year olds				
1996	30	70	91.3	87.2 to 94.0
1997	135	271	89.5	86.6 to 91.8
1998	58	80	73.2	60.0 to 82.0
9 to 13 year olds				
1996	44	68	85.5	78.7 to 90.1
1997	218	361	82.6	78.1 to 86.2
1998	132	148	55.4	34.6 to 69.6