Copyright Statement

The digital copy of this thesis is protected by the Copyright Act 1994 (New Zealand).

This thesis may be consulted by you, provided you comply with the provisions of the Act and the following conditions of use:

• Any use you make of these documents or images must be for research or private study purposes only, and you may not make them available to any other person.
• Authors control the copyright of their thesis. You will recognise the author’s right to be identified as the author of this thesis, and due acknowledgement will be made to the author where appropriate.
• You will obtain the author's permission before publishing any material from their thesis.

To request permissions please use the Feedback form on our webpage. http://researchspace.auckland.ac.nz/feedback

General copyright and disclaimer

In addition to the above conditions, authors give their consent for the digital copy of their work to be used subject to the conditions specified on the Library Thesis Consent Form.
THE EPIDEMIOLOGY OF PERTUSSIS IN NEW ZEALAND AND RISK FACTORS FOR PERTUSSIS IN NEW ZEALAND INFANTS

VOLUME 1 (TEXT)

Cameron Charles Grant

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Paediatrics and Epidemiology, The University of Auckland, Auckland, New Zealand, March 2004
THE EPIDEMIOLOGY OF PERTUSSIS IN NEW ZEALAND AND RISK FACTORS FOR PERTUSSIS IN NEW ZEALAND INFANTS

VOLUME 2 (TABLES, FIGURES AND APPENDICES)

Cameron Charles Grant

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Paediatrics and Epidemiology, The University of Auckland, Auckland, New Zealand, March 2004
ACKNOWLEDGEMENTS

I wish to acknowledge:

- All of the families of infants who participated in this study.
- All of the people who worked on research projects that contributed to this thesis including the interviewers, research nurses, project manager, the nurses and doctors at Starship Children's Hospital, Middlemore Hospital and Christchurch Public Hospital, the microbiology laboratory staff at Auckland and Middlemore Hospital, the virology and immunology laboratory staff at Auckland hospital, the summer research students, the community steering committee and the investigators.
- To the National Child Health Research Foundation, the Health Research Council of New Zealand and the Royal Australasian College of Physicians for research grants that contributed to this thesis.
- Professor Diana Lennon for encouraging me to study pertussis and Professor John Boulton for encouraging me to complete this work as a PhD thesis.
- My two PhD supervisors Associate Professor Robert Scrapp and Associate Professor Mark Thomas for all of their encouragement, knowledge and time.
- To my family for all of their time, all of their tolerance and all of their patience.
PREFACE

Pertussis was devastating in the pre-immunisation era and continues to kill infants. It is a disease against which the successes of immunisation have been considerable but have been clouded by controversies relating to the vaccines used. In contrast to other vaccine preventable diseases, pertussis cannot currently be eradicated by immunisation. New Zealand experiences a disproportionately large disease burden from pertussis.

The epidemiology of pertussis is complex and has been modified substantially by immunisation. In this thesis the epidemiology of pertussis in the pre-immunisation era and since mass immunisation will be described with the New Zealand literature compared with that from other developed countries. This literature review will identify the current limitations in our knowledge of pertussis epidemiology in New Zealand and in our knowledge of the risk factors for pertussis both in New Zealand and internationally.

The research questions generated will then be answered from a historical review of New Zealand pertussis epidemiology and a contemporary case control study of risk factors for pertussis in infants.

Following a discussion of the strength and weaknesses of the study and of the study findings, recommendations will be made on how immunisation coverage and pertussis control can be improved and on potential future directions for research on pertussis and immunisation.
ABSTRACT

Literature review

Pertussis mortality and morbidity
Mass immunisation was associated with a decrease in pertussis mortality and a profound reduction in pertussis incidence. Despite this pertussis remains prevalent. Infants account for the majority of pertussis deaths and hospitalisations.

Immunisation
Pertussis vaccines protect against disease rather than infection. Despite immunisation pertussis remains endemic. The efficacy of different whole cell and acellular pertussis vaccines varies considerably.

There has only been a small increase in immunisation coverage in New Zealand over the past 25 years. Currently between 80% and 90% of New Zealand children receive the primary immunisation series.

Other epidemiological features
* Bordetella pertussis* is a highly infectious organism. Neither infection nor immunisation results in lifelong immunity. Pertussis affects all age groups. It is more severe in females than in males. The incidence has always been highest in infants and children but the reported incidence in adults is increasing. Pertussis epidemics occur at four yearly intervals. The epidemic periodicity has not been changed by immunisation.

Risk factors for pertussis
Contemporary case control studies from the United States have shown that exposure to someone outside of the home with pertussis increases the risk of introduction of pertussis into the home and that infants of adolescent mothers and of mothers with a preceding coughing illness are at increased risk of pertussis. Small sample size and imprecise measurement of immunisation status have compromised these studies.

Other factors associated with an increased risk of pertussis in infants include younger age, low birth weight, the infant's immunisation status and household crowding.
Prior to this current case control study there was no knowledge on the effect of infant characteristics, infant immunisation status, parental and household characteristics, or socioeconomic factors on the risk of pertussis in infants.

**Methods**

The pertussis mortality and hospital discharge statistics and notification data from 1872 to 2000 were reviewed. The characteristics of children hospitalised with pertussis during the 1995 to 1997 epidemic were described. Risk factors for pertussis in infants were determined using a case control study with two different control groups. A matched case-control design was used to compare infants with pertussis with well control infants from the community. An unmatched design was used to compare infants hospitalised with pertussis to infants hospitalised with other acute respiratory illnesses.

**Results**

**Historical review of pertussis epidemiology**

Immunisation was associated with a significant decline in pertussis mortality rates in New Zealand. Pertussis incidence rates in New Zealand are five and 10 times higher than in the United Kingdom or the United States.

New Zealand pertussis hospital discharge rates increased from 1920 to 1950, decreased from 1950 to 1970 and have been increasing since then. The severity of disease among those hospitalised in New Zealand is comparable to other developed countries.

**Case control study of risk factors for pertussis in infants**

In the community control sample factors associated with incomplete immunisation included poverty and household crowding, advice from a doctor that immunisations be delayed and the caregiver not having a record of the infant's immunisations.

Primary and secondary pertussis in case households occurred in all age groups. Over half of the primary cases were infants.

Factors associated with an increased risk of pertussis included incomplete immunisation of the infant, children five to nine years of age living in the household, household members with pertussis during the preceding two months and the family doctor advising that an immunisation be delayed.
Preschool attendance by a household member was associated with a decreased risk of pertussis. Infants of low birth weight and infants with younger mothers were not at increased risk of pertussis.

In a multivariate analysis, non-immunisation of other children in the household and the presence of someone in the household with clinical pertussis were associated with an increased risk of pertussis in infants.

The associations between household members with cough and the risk of pertussis varied with the age of the household members and imply an age dependent disease modifying effect of immunisation.

For many of the children in the study households it seems unlikely that any health professional knew whether or not they were fully immunised.

Conclusions

Immunisation reduced pertussis mortality in New Zealand. Pertussis hospitalisation rates are increasing despite improvements in the immunisation schedule. Sustained sub-optimal immunisation coverage appears to be the dominant reason for New Zealand's excessive pertussis disease burden. Primary school aged children are important in household pertussis transmission.
# TABLE OF CONTENTS (VOLUME 1)

Chapter 1. Pertussis mortality .............................................. 1  
1.1 Aims of chapter ......................................................... 1  
1.2 Pertussis mortality in developed countries .......................... 1  
1.3 Changes in pertussis case fatality rates in developed countries 4  
1.4 The number of pertussis deaths in recent years ........................... 5  
1.5 Epidemiological features of fatal pertussis ............................ 6  
1.6 Limitations to estimates of pertussis mortality ........................ 7  
1.7 Chapter summary ..................................................... 10  

Chapter 2. Pertussis morbidity .............................................. 13  
2.1 Aims of chapter ......................................................... 13  
2.2 Limitations in estimating pertussis incidence .......................... 13  
2.3 Pertussis incidence ......................................................... 21  
2.4 Pertussis morbidity as defined by hospitalisation data .............. 23  
2.5 Chapter summary ..................................................... 28  

Chapter 3. Immunisation ....................................................... 31  
3.1 Aims of chapter ......................................................... 31  
3.2 Development of pertussis vaccines .................................... 32  
3.3 Immunisation schedules .................................................. 35  
3.4 Vaccine efficacy ........................................................... 39  
3.5 Adverse reactions following pertussis immunisation .................. 49  
3.6 Factors associated with incomplete immunisation ..................... 54  
3.7 Immunisation coverage .................................................... 58  
3.8 Chapter summary ..................................................... 67  

Chapter 4. Other epidemiological features .................................. 72  
4.1 Aims of chapter ......................................................... 72  
4.2 Age ........................................................................ 72  
4.3 Gender ................................................................. 78  
4.4 Temporal variations in pertussis incidence .............................. 80  
4.5 Organism, infectivity and immunity following infection ............ 82  
4.6 Socioeconomic status and ethnicity ..................................... 85  
4.7 Chapter summary ..................................................... 86  

Chapter 5. Risk factors for pertussis in infants ............................. 91  
5.1 Aims of chapter ......................................................... 91  
5.2 Contemporary studies of the risk factors for pertussis ................. 91  
5.3 Factors associated with an increased risk of pertussis in infants .... 97  
5.4 Chapter summary ..................................................... 106  

Chapter 6. Pertussis epidemiology in New Zealand ......................... 109  
6.1 Aims of chapter ......................................................... 109
6.2 Early history of epidemic disease in New Zealand ........................................ 109
6.3 Pertussis mortality in New Zealand .................................................................. 111
6.4 Pertussis morbidity in New Zealand ................................................................. 113
6.5 Chapter summary .............................................................................................. 122

Chapter 7. Pertussis and immunisation in New Zealand ........................................ 126
7.1 Aims of chapter .................................................................................................. 126
7.2 Primary care in New Zealand ........................................................................... 127
7.3 Health policy and immunisation ...................................................................... 130
7.4 Immunisation delivery in New Zealand ......................................................... 136
7.5 Immunisation schedules in New Zealand ...................................................... 137
7.6 Pertussis vaccine efficacy in New Zealand ...................................................... 139
7.7 Pertussis vaccine coverage in New Zealand ................................................... 142
7.8 Factors associated with incomplete immunisation in New Zealand ............... 147
7.9 How immunisation coverage can be improved in New Zealand ..................... 153
7.10 Chapter summary ............................................................................................ 157

Chapter 8. Comparisons between New Zealand and other developed countries .... 163
8.1 Aims of chapter .................................................................................................. 163
8.2 Comparison of pertussis epidemiology in New Zealand with other developed countries .................................................................................................................................................. 163
8.3 Comparison of immunisation in New Zealand with other countries ............... 169
8.4 Comparison of risk factors for pertussis in infants in New Zealand with other developed countries .................................................................................................................................................. 172
8.5 Chapter summary .............................................................................................. 173

Chapter 9. Research objectives, questions and hypotheses .................................... 178
9.1 Aims of chapter .................................................................................................. 178
9.2 Research objectives ........................................................................................... 178
9.3 Research questions and hypotheses on pertussis epidemiology ....................... 178
9.4 Research questions and hypotheses to be answered on risk factors for pertussis in infants .................................................................................................................................................. 181

Chapter 10. New Zealand historical data ............................................................... 185
10.1 Aims of chapter .................................................................................................. 185
10.2 New Zealand demographic, mortality and morbidity data .............................. 185
10.3 Time periods over which data were available on specific variables ............... 189
10.4 Calculation of rates .......................................................................................... 194
10.5 Chapter summary .............................................................................................. 197

Chapter 11. Case control analysis of risk factors for pertussis in infants .................. 199
11.1 Aims of chapter .................................................................................................. 199
11.2 Epidemiological principles ............................................................................. 200
11.3 Research design ............................................................................................... 202
11.4 Definitions and measurements ....................................................................... 213
21.5 Barriers to taking infants to the general practitioner .................................................. 349
21.6 Doctor advising and caregiver requesting that immunisations be delayed .......... 350
21.7 Multivariate analysis of the relationship with primary care and the risk of pertussis .......................................................... 351
21.8 Chapter summary ............................................................................................................. 352
21.9 Conclusion ...................................................................................................................... 353

Chapter 22. Multivariate analysis of risk factors for pertussis .............................................. 354
22.1 Aims of chapter ............................................................................................................... 354
22.2 Criteria for inclusion of variables in the multivariate models ........................................ 354
22.3 Multivariate models ........................................................................................................ 357
22.4 Multivariate analyses of risk factors for pertussis in comparison with the community controls ........................................................................................................... 358
22.5 Multivariate analyses of risk factors for pertussis in comparison with the hospital controls ................................................................................................................... 361
22.6 Summary .......................................................................................................................... 364
22.7 Conclusion ...................................................................................................................... 366

Chapter 23. Pertussis epidemiology ......................................................................................... 367
23.1 Aims of chapter ............................................................................................................... 367
23.2 Decline in pertussis mortality rates in New Zealand over time ..................................... 367
23.3 Impact of immunisation on mortality rates .................................................................... 368
23.4 Pertussis case fatality rates in New Zealand .................................................................. 369
23.5 Other epidemiological features of pertussis mortality ...................................................... 370
23.6 Periodicity of pertussis epidemics in New Zealand ........................................................ 371
23.7 Trends in pertussis hospitalisations in New Zealand over time ...................................... 372
23.8 Comparison of pertussis hospital discharge rates in New Zealand with other countries .................................................................................................................................. 375
23.9 Hospital discharge rates by gender and ethnicity and length of stay in hospital .......... 376
23.10 Chapter summary ......................................................................................................... 378

Chapter 24. Biases in the case control analysis ...................................................................... 381
24.1 Aims of chapter ............................................................................................................... 381
24.2 Biases in pertussis cases ................................................................................................. 381
24.3 Biases in community controls ....................................................................................... 386
24.4 Biases in hospital controls ............................................................................................. 391
24.5 Summary ........................................................................................................................ 393

Chapter 25. Risk factors for incomplete immunisation and risk factors for pertussis in infants ........................................................................................................................................ 397
25.1 Aims of chapter ............................................................................................................... 397
25.2 Immunisation in the community controls ...................................................................... 399
25.3 Primary and secondary transmission in households ....................................................... 402
25.4 Infant characteristics, visits out of the home and immunisation status ...................... 404
ABBREVIATIONS

CDC  Centers for Disease Control
CI   Confidence interval
CPHA-PAS  Commission on Professional and Hospital Activities-Professional Activities Survey
DT   Diphtheria-tetanus
DTaP  Acellular diphtheria-tetanus-pertussis
DTP  Diphtheria-tetanus-pertussis
FHA  Filamentous hemagglutinin
FIM  Fimbrial agglutinin
GDP  Gross domestic product
ICD  International classification of diseases, injuries and causes of death
ICD-9 CM  International classification of diseases, injuries and causes of death, ninth revision clinical modification
IgA  Immunoglobulin class A
IgG  Immunoglobulin class G
NZSEI  New Zealand socioeconomic index score
OECD  Organisation for Economic Co-operation and Development
OPV  Oral polio vaccine
OR   Odds ratio
PCR  Polymerase chain reaction
PRN  Pertactin
PT   Pertussis toxin
RR   Relative risk
UNICEF  United Nations Children's Fund
WHO  World Health Organization
s.d.  Standard deviation
SPSS  Supplementary Pertussis Surveillance System
vs.  Versus